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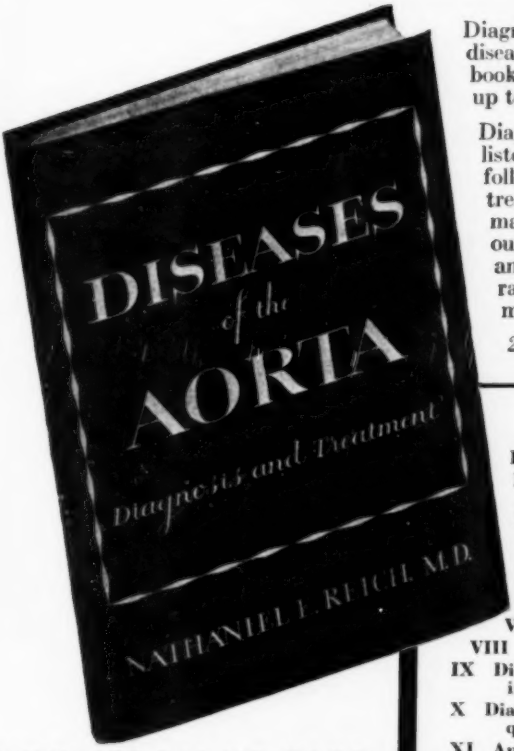

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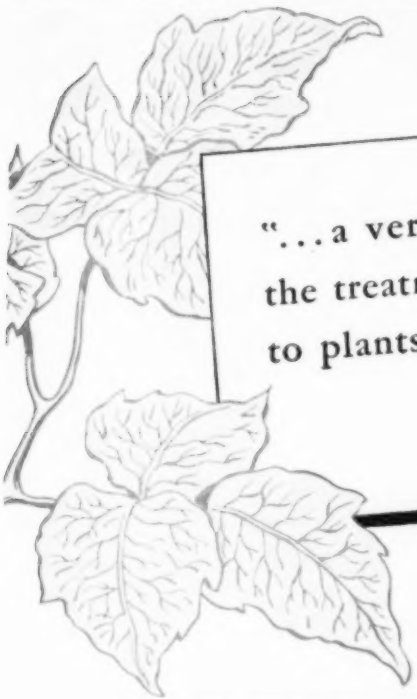

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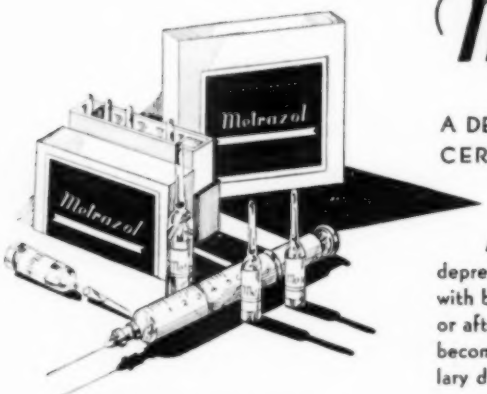

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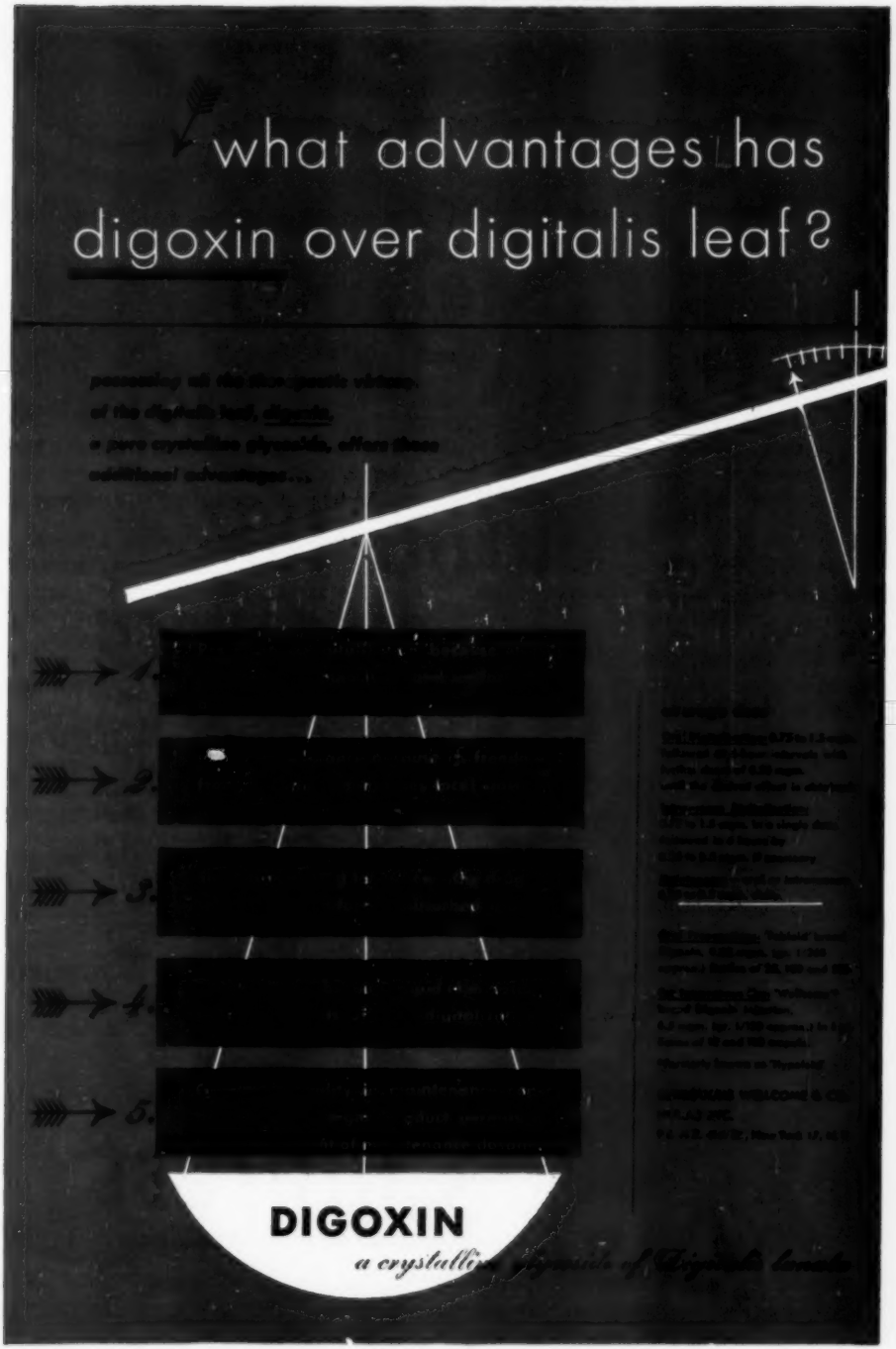
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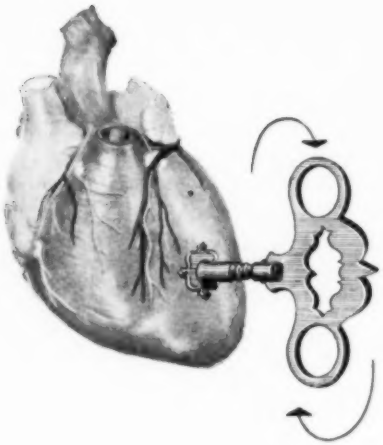

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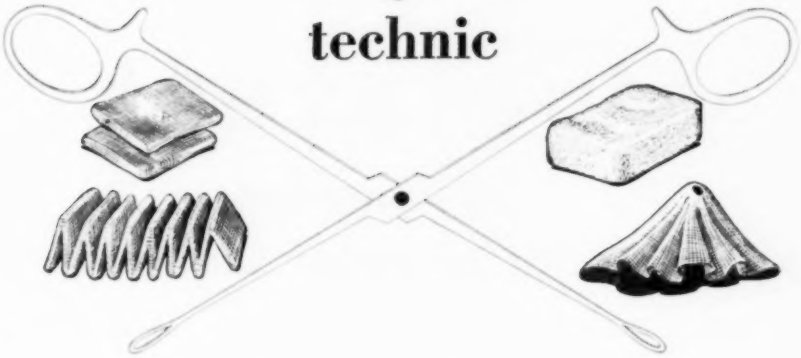

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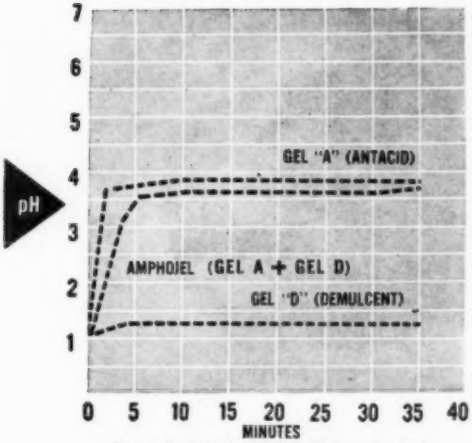

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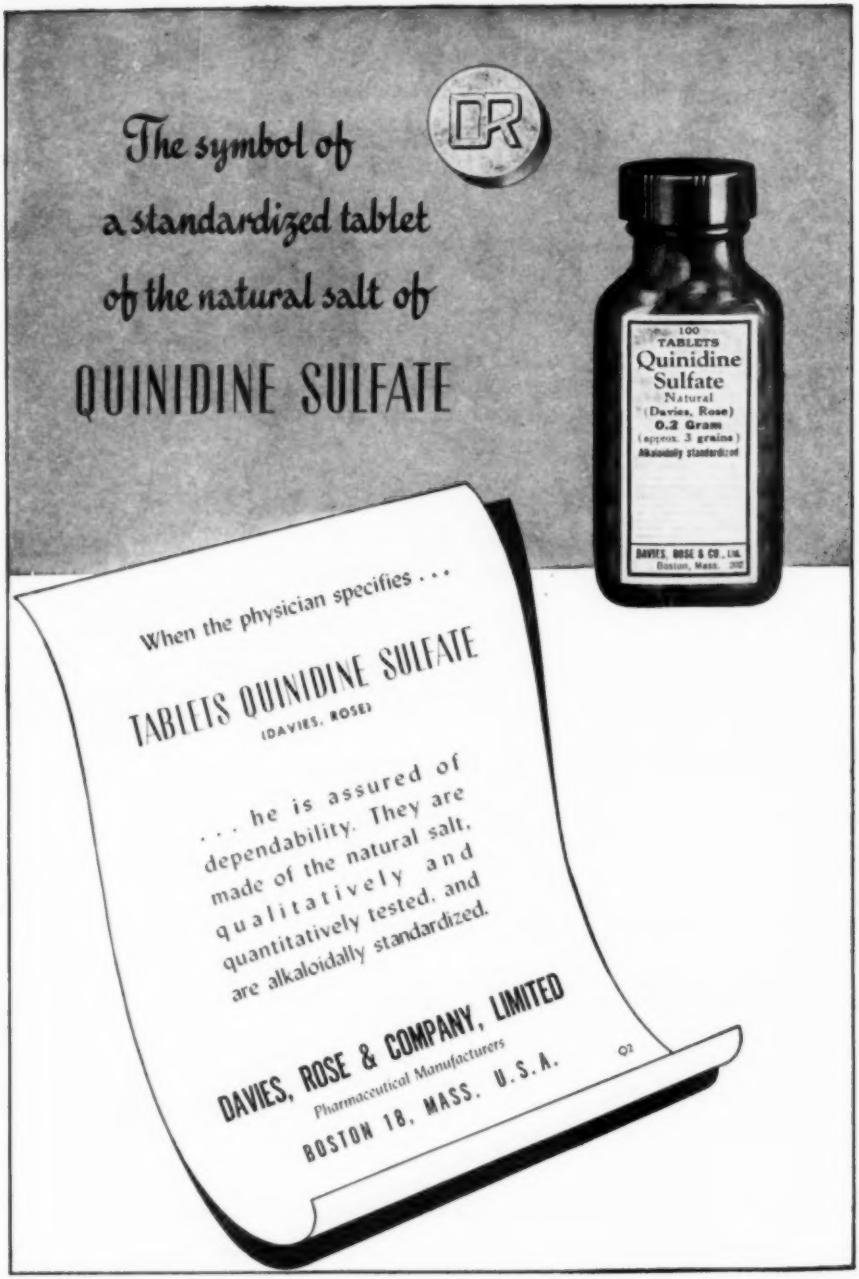
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Liver Fractions from	*36.0 Gm. liver*

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1. Brown, G. O.: Postgraduate Med. 4:203, 1948.
2. White, B. V.: Amer. Practitioner 8:709, 1948.
3. Morrison, L. M.: J. A. M. A. 134:678, 1947.
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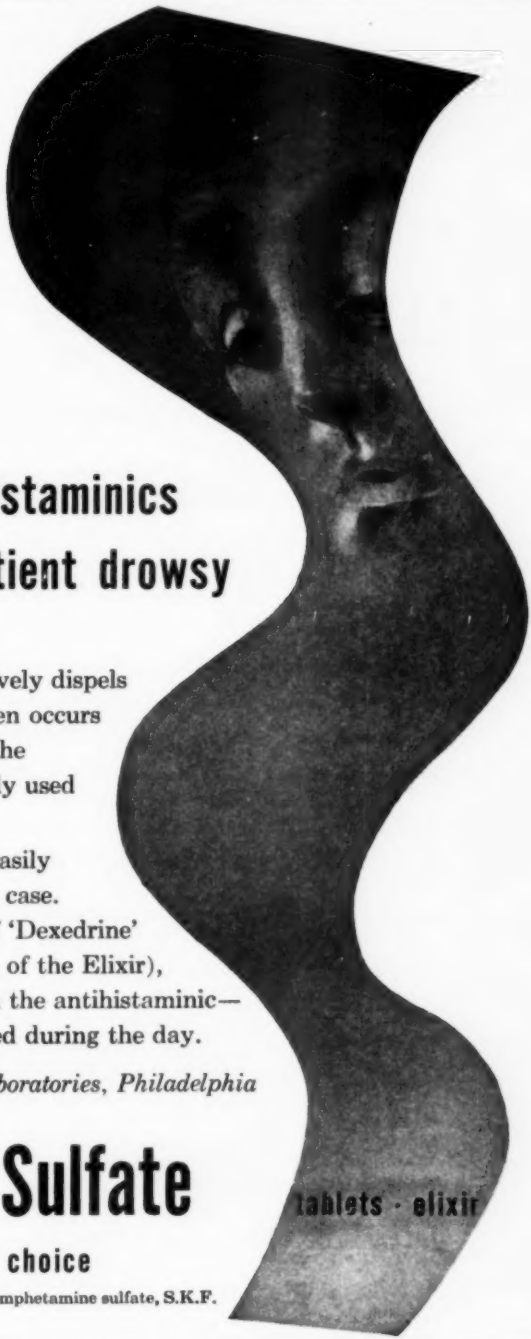

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1. Rakoff, A. E., Paschkis, K. E. and Cantarow, A.: J. Clin. Endocrinol. 7:688 (Oct.) 1947.
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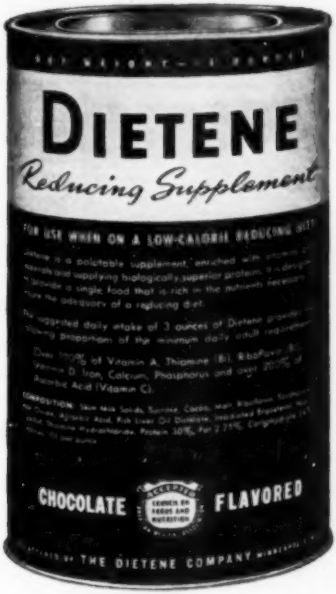

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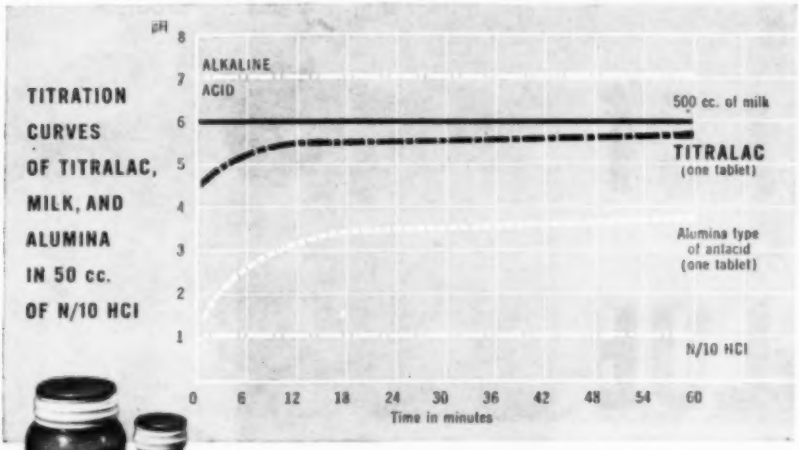

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REFERENCES

1. Rossett, N. E., and Flexner, J.: Ann. Int. Med. 18: 193 (1944). 2. Freezer, C. R. E.; Gibson, C. S., and Matthews, E.: Guy's Hosp. Reports 78: 191 (1928). 3. Aaron, A. H.; Lipp, W. F., and Milch, E.: J. A. M. A. 139: 514 (Feb. 19) 1949. 4. Kirsner, J. B., and Palmer, W. L.: Illinois M. J. 94: 357 (Dec.) 1948. 5. Kimball, S.: in Practice of Medicine (Tice). Hagerstown, Md., W. F. Prior Company, Inc., 1948, p. 210. 6. Special Article: M. Times 76: 10 (Jan.) 1948.

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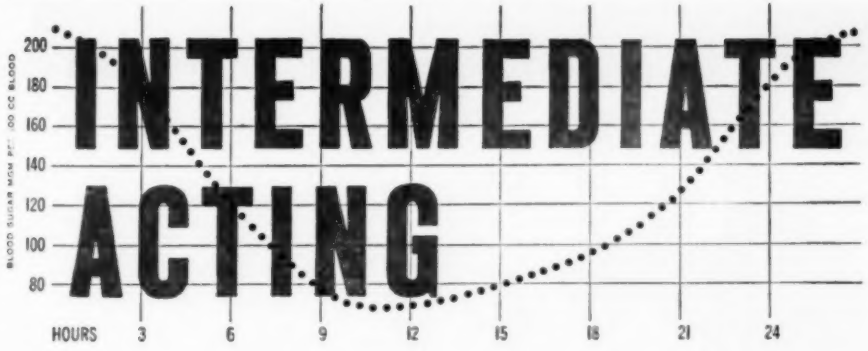

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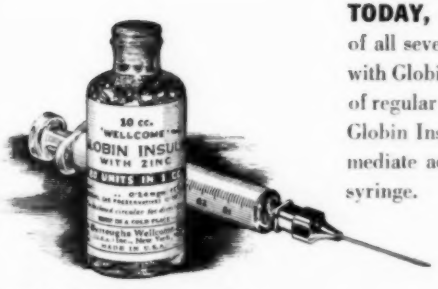

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
2. Ibid Proc. Am. Diabetes Assn. 8:37, 1948.

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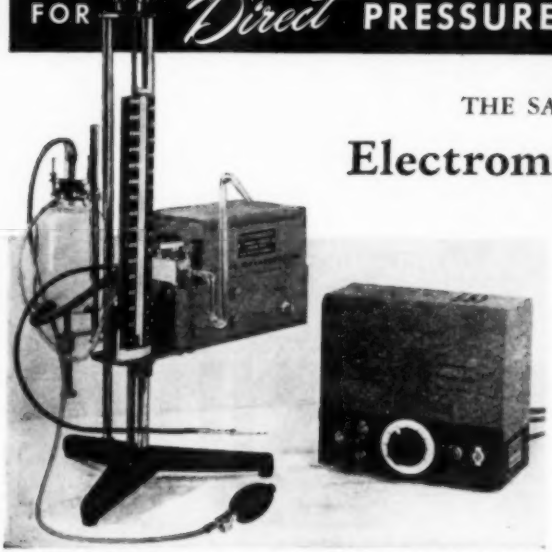

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The Electromanometer has a wide range of sensitivity. The most sensitive range is 5 centimeters per 1.0 millimeter of mercury pressure change. The least sensitive is 5 centimeters deflection per 400 millimeters of mercury pressure change. The in-between sensitivity positions are: 2.0, 4.0, 10, 20, 40, 100 and 200 millimeters of mercury pressure change to produce a 5.0 centimeter deflection of the recording galvanometer.

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1. Ivy, A. C., and Goetzl, F. R. (1945), d-Desoxyephedrine; A Review, War Med., 7:60, January.
2. Davidoff, E. (1945), A Comparison of the Stimulating Effect of Amphetamine, Dextroamphetamine and Dextro-N-Methyl Amphetamine (Dextro-Desoxyephedrine), Med. Rec., 156:422, July.

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Stable without refrigeration, LYOVAC *Normal Human Plasma (Irradiated)* is prepared according to regulations of the National Institute of Health. The plasma is pooled, flash-frozen, dehydrated from the frozen state under high vacuum (the lyophile process) and sealed under vacuum.

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Gamma Globulin, 660 mg./100 cc.

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ANNALS OF
INTERNAL MEDICINE

VOLUME 31 SEPTEMBER, 1949 NUMBER 3

PHEOCHROMOCYTOMA: DIAGNOSIS AND TREATMENT *

By GEORGE F. CAHILL, M.D., and HENRY ARANOW, JR., M.D.,
New York, N. Y.

PHEOCHROMOCYTOMAS are relatively rare tumors of the chromaffin sympathetic nerve tissue, usually producing epinephrine, and/or, norepinephrine and most often seen in the adrenal medulla or in one of the many areas where chromaffin tissue occurs.[1, 2] The usual symptoms produced by the tumor are the result of the secretion of an excess of epinephrine or some other allied pressor substance, either intermittently or continuously. The action of epinephrine is hemodynamic and metabolic. The hemodynamic changes have a short latent period, a dependence of the magnitude of response upon the dose, and a rapid return to normal. They are a constriction of the peripheral arterioles with elevation of the blood pressure followed by a rise in cardiac output. The chief metabolic changes are increases in blood sugar, blood lactic acid and basal metabolic rate. These excess secretions of a pressor substance, if only occasional, may have no other effect upon the individual, but if frequent or continuous, may show the subsequent effect seen with continuous elevation of the blood pressure. From this it would seem that the syndrome is sufficiently distressing and that the symptoms are so characteristic that the diagnosis would be apparent. In fact, however, many of these cases are seen and treated without the correct diagnosis or the discovery of the cause.

The symptoms first described and most characteristic of the syndrome are the attacks of paroxysmal hypertension. On the other hand persisting unremitting hypertension has been shown to occur with some tumors, either developing from the intermittent hypertension or being unremitting from the onset. Some tumors of pheochrome tissue, rarely in the abdomen or chest

* Presented at the Thirtieth Annual Session of the American College of Physicians, March 29, 1949, New York, N. Y.

From the Departments of Urology and Medicine, Columbia-Presbyterian Medical Center, New York City.

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but especially in the carotid body, apparently do not cause the hypertensive symptoms.

Tumors have been found in the following types of cases:

(1) A symptom-free individual with a tumor discovered accidentally or at autopsy.

(2) A symptom-free individual with sudden death following a minor trauma, frequently a surgical operation and the tumor discovered on autopsy.

(3) The adrenal sympathetic syndrome.

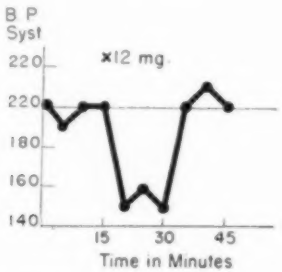

FIG. 1. Positive test in a case of pheochromocytoma with 12 mg. of benzodioxane.

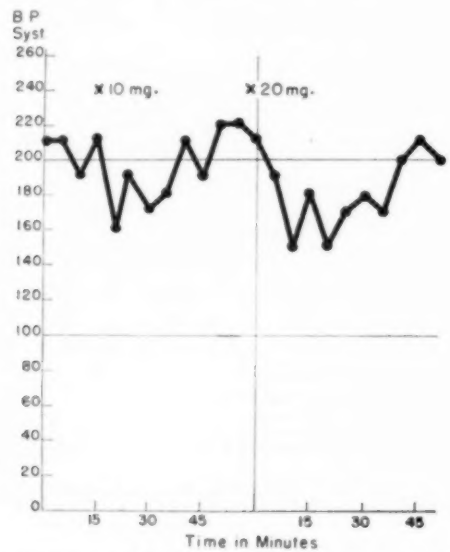

FIG. 2. Positive tests in a case of pheochromocytoma with 10 mg. and 20 mg. intravenous injection of benzodioxane.

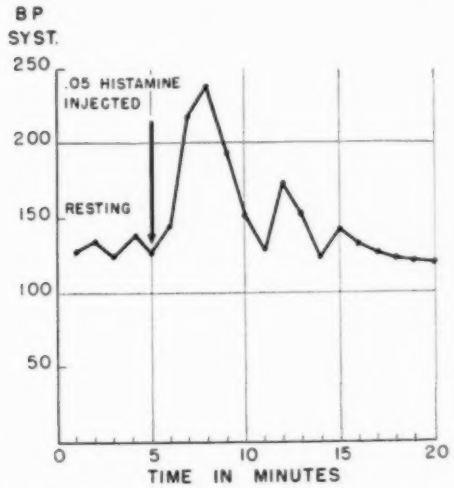

FIG. 3. Positive test in a case of pheochromocytoma with .05 mg. histamine base.

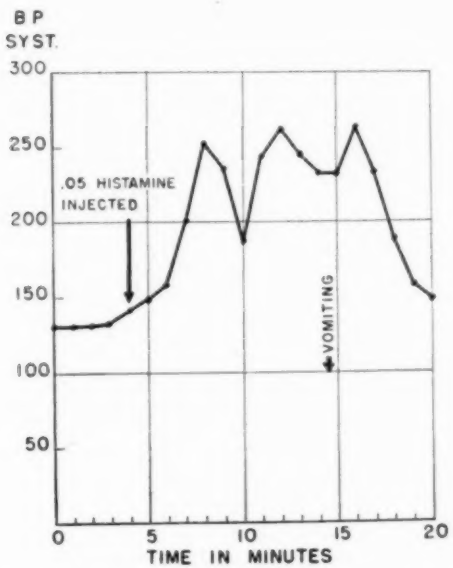

FIG. 4. False positive test with .05 mg. histamine base, in a case of psychoneurosis with hypertension. No tumor found on operative exploration.

(A) With usually a normal blood pressure but with intervals of paroxysmal hypertension.

(B) A continuous hypertension with paroxysmal rises.

(4) A continuous hypertension simulating an essential or malignant hypertension.

When the disease occurs and is suspected, the diagnosis may depend upon the following.

(1) A typical attack and associated clinical findings.
(2) Demonstration in the blood of a pressor substance, epinephrine, in a syndrome case as shown by Beer, King and Prinzmetal.[3]
(3) The showing of a significant reduction of the blood pressure in a hypertensive state, either continuously or paroxysmally, by an epinephrine antagonist such as benzodioxane or with dibenamine.
(4) Precipitation of an attack of hypertension in a resting stage case, by an epinephrine secretion provocative such as histamine or mecholyl.
(5) Roentgenographic evidence of the presence of a tumor either within or without the adrenal as shown without or with air insufflation or by renal displacement as shown with pyelographic media.

Symptoms and Associated Findings

The sudden death that still occurs in individuals with unsuspected tumors emphasizes the fact that because of their rarity many of these tumors are still missed. The symptom described as paroxysmal hypertension is not always indicative of a tumor of the chromaffin system. According to Bauer and Belt,[4] such crises have been observed in eclampsia, lead poisoning, essential hypertension, nephritis, aortitis and various diseases of the nervous system such as epilepsy, traumatic or vascular damage to the brain or meninges. Rowntree and Ball [5] reported a case of tabes with paroxysmal elevation of the systolic blood pressure, which was explored for adrenal tumor and no tumor found either by exploration or at autopsy. Wells and Boman [6] state that the common and most likely clinical diagnostic errors have been "essential hypertension, cardiac neurosis, hyperthyroidism, diabetes mellitus and renal tumor." The differential diagnosis between psychoneurosis and hysteria accompanied by some hypertension has presented many difficulties in considering, in such cases, whether a pheochromocytoma may be present. In the last few years we at the Columbia Presbyterian Medical Center have explored 14 such cases without finding any tumor. The explored cases all had peculiar sensations of precordial distress, heart pounding, numbing and tingling of the extremities and some had glycosuria. A negative response was obtained in all of the cases to the epinephrine antagonist, benzodioxane, in which it was used, but at that time its value as a diagnostic aid had not been established. All of these cases had no recognizable change in

the adrenals by air insufflation roentgen-rays. The operative explorations were performed to establish the diagnosis and in the hope of finding a tumor outside the adrenal and with atypical symptoms. A similar experience has been discussed by Van Epps et al.[7] Rarely there appear in children, cases

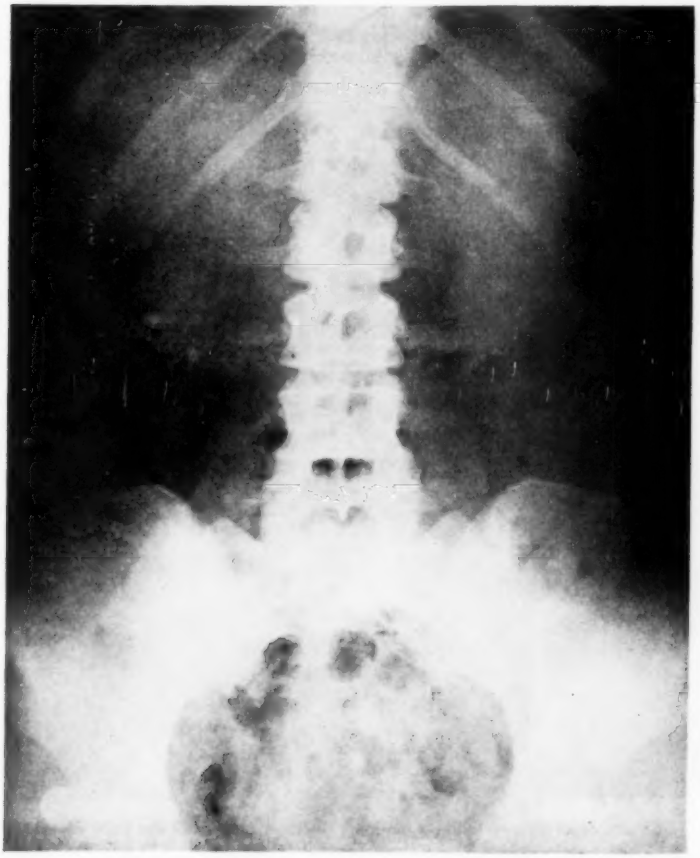

FIG. 5. Intravenous urogram showing iodide solution in the pelvis of the right kidney with a rounded tumor mass above the right kidney. The tumor mass was a pheochromocytoma.

with almost typical symptoms of paroxysmal crises, with associated metabolic changes and blood pressure changes suggestive of a positive reaction to benzodioxane, with no tumor disclosed either by roentgen-ray or by operation. These cases have resembled the case reported by Penfield[8] of tumor

of the diencephalon, but without the symptoms of intracranial pressure. Whether an undisclosed lesion of the diencephalon is responsible for such phenomena awaits study.

In the cases in which the tumor has been proved and the attacks are intermittent, the usual presenting evidence has been the acute unpredictable attacks lasting a few seconds to several hours. In the attack the palpitation distress may overshadow the other symptoms. Since the effect of excess epinephrine is both upon the peripheral resistance and upon the cardiac

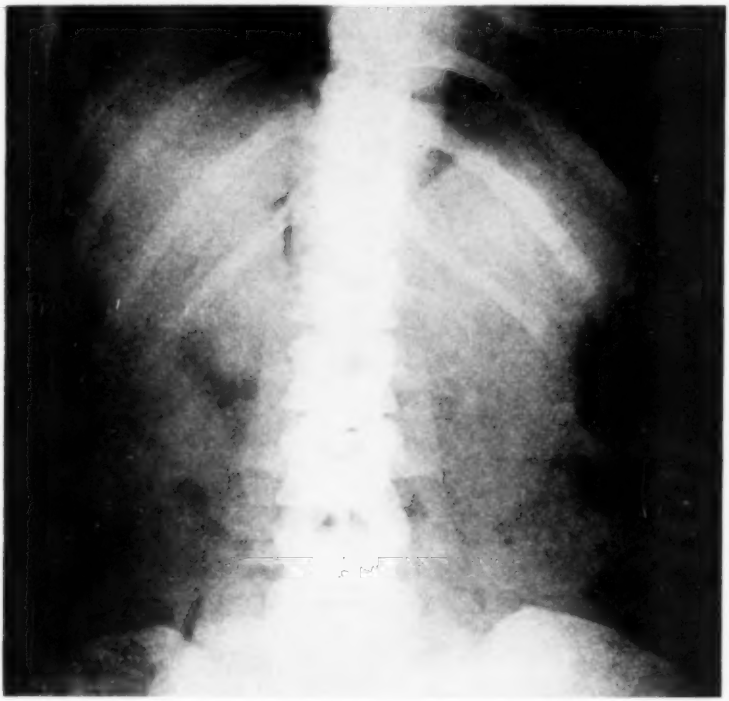

FIG. 6. Same case as figure 5 with air outlining the upper portion of the right adrenal tumor.

output, the pale and cold extremities may precede the palpitation. The cessation of the attack is accompanied by excessive sweating. We have never seen a tumor case with symptoms that did not have excessive sweating. The hypertensive attacks are mostly similar each time but with gradually increasing severity and frequency, progressing with the increasing size of the tumor. The amount of exhaustion following the attack is dependent upon its duration and if long drawn out may in time progress into shock.

Persistent hypertension with paroxysmal crises may occur. In Green's[9] review of 51 cases, 14 only showed intermittent hypertension and 37 had more or less continuous hypertension. Goldenberg et al.[10] quote Smithwick in which he found pheochromocytoma in 0.5 per cent of 1000 cases of hypertension subject to lumbo-dorsal sympathectomy. In any hypertensive that has paroxysmal crises, the possibility of a pheochromocytoma should be suspected, especially if any of the associated metabolic findings are present.

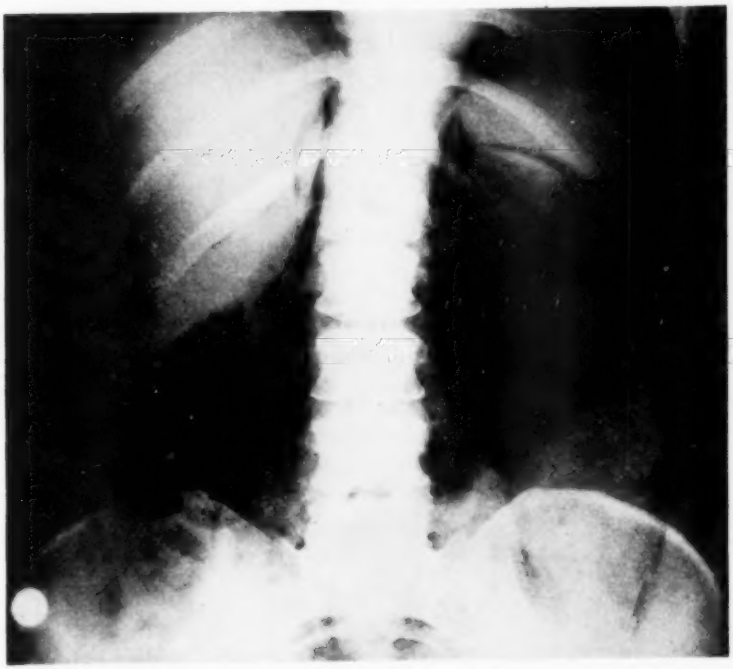

FIG. 7. Air insufflation roentgenograms with air in both adrenal fascial planes. The queer-shaped right area denser than normal proved to be only cortical tissue on a long ovoid cystic pheochromocytoma that filled the area also surrounded with air.

It is in this type of case that the use of epinephrine antagonists has proved helpful in the diagnosis.

The presence of permanent hypertension undistinguishable from essential or malignant hypertension in some of these cases has led Thorne [11] to suggest that each patient with severe hypertension be investigated for the presence of pheochromocytoma since removal of such a tumor gives one the opportunity of really curing a hypertension. Continuous unremitting hypertension has been reported with pheochromocytoma by Palmer and Castleman,[12]

Binger and Craig [13]; Phillips,[14] Kirschbaum and Balkin [15]; McCullagh and Engel [16]; Thorn, Hindle and Sandmeyer,[11] Goldenberg, Snyder and Aranow,[10] Ganem and Cahill [17] and by Cahill.[18]

When paroxysmal hypertensive crises occur they are usually accompanied by paroxysmal hyperglycemia. In three children with tumor reported by ourselves, no hyperglycemia was observed. The children also had in addition a more or less persistent hypertension. The failure to

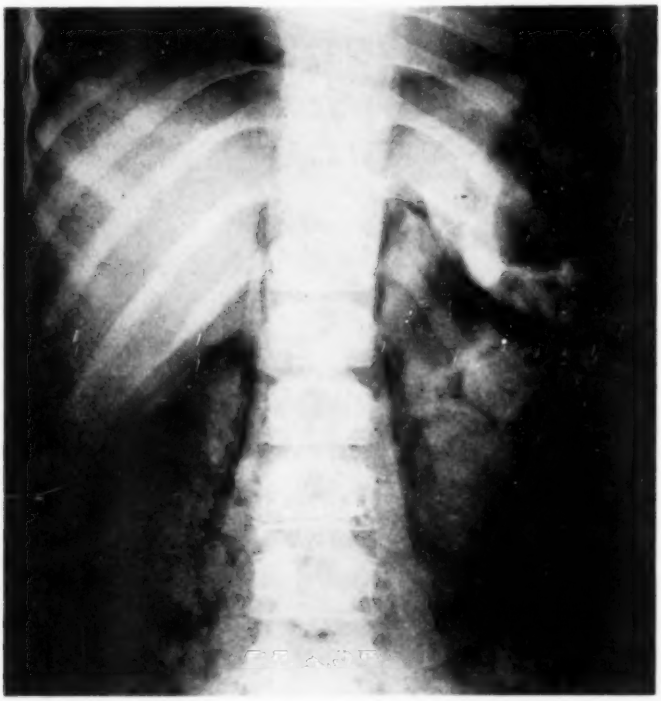

FIG. 8. An air insufflation roentgenogram in a child with a pheochromocytoma of the left adrenal. The right adrenal is clearly shown as a long narrow gland. The left is the ovoid tumor shadow above the left kidney.

observe hyperglycemia in these children has been attributed to the relatively low glycogen storage in the liver in children. Hyperglycemia has also been reported as absent in a number of cases in adults, by Van Epps et al.,[7] and by Engle, Mencher and Engel.[20] It seems to be mostly present in adults with the exception of the few cases above reported. In cases with continuous hypertension a more or less persistent hyperglycemia and glycosuria may occur as was shown by Duncan, Semans and Howard.[19] The hypergly-

cemias may often show extreme fluctuations. The glucose tolerance tests have marked variations but as a rule the tolerance is usually low. Thorn, Hindle and Sandmeyer [11] report in a tumor with persistent hypertension a glucose tolerance test that was high, the opposite to that usually seen. Clinically some of these cases may resemble the usual variety of diabetes as was shown by deVries et al.[21] Hypertensive crises with paroxysmal hyperglycemia and transitory glycosuria are not indicative of pheochromocytoma only, but may occur in other conditions.

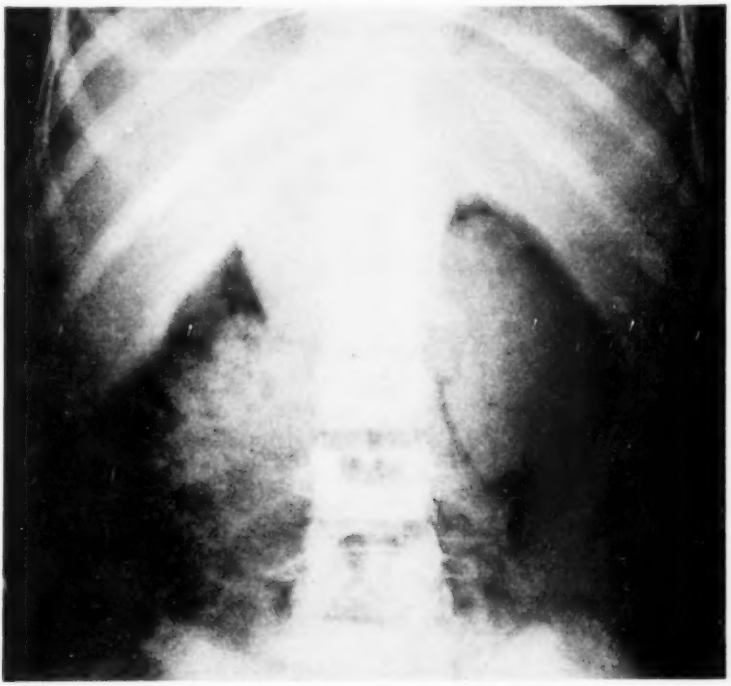

FIG. 9. An air insufflation roentgenogram in a child with a large tumor between the vena cava and the aorta just below the liver. The air infiltrated around the left kidney which is normal but was unable to infiltrate on the right side. The air outlines the edge of the large tumor, just to the right of the vertebral column.

The effect of the excess epinephrine upon the glycogen from the liver may be shown by the estimation of the blood sugar and be of value in the diagnosis but the effect of the epinephrine upon the muscle tissue and the production of lactic acid with increase in the blood has not apparently been of use clinically for diagnostic purposes. Hypermetabolism can easily be shown to be present by the elevation of the basal metabolic rate. The ele-

vation may suggest and has been often suspected by being associated with hyperthyroidism but the differential diagnosis may be helped by the calculation of the blood iodine level or of the uptake of radio iodine by the thyroid gland. The discussion of Wells and Boman,[6] following the suggestion of McQuarry that aid to the diagnosis might be given by determinations of the blood potassium during attacks, has apparently not been of use.

Demonstration of Pressor Substances in the Blood

By chemical analysis Ernould and Picard [22] in 1934 showed that there was a pressor substance in the blood during a hypertensive crisis. Beer,

Fig. 10. Roentgenogram of chest in boy who had a pheochromocytoma removed from his abdomen. The abdominal tumor was on the right side and not adrenal and produced symptoms. This tumor in the right superior mediastinum was asymptomatic; discovered by accident and removed surgically. It also was a pheochromocytoma.

King and Prinzmetal [3] reported in 1937 the presence of a pressor substance, probably epinephrine, in the blood during a hypertensive crisis. They used a modification of Pissemski's method with perfusion of the denervated ear of a rabbit and were able to show a reversal effect upon the reading with ergotamine. Such a demonstration has been done only rarely probably due to the difficulties of the test and the special technical facilities necessary; the

specificity of these methods too has been questioned by the work reported by Kreuzfeldt.[23]

Use of Epinephrine Antagonists

Of the large number of benzodioxanes first investigated by Fourineau and Bovet in 1935, two were selected by Goldenberg et al.[10] for study and for the purpose of devising a simple test to demonstrate the presence of excess epinephrine. Using 933 F and 1164 F, they were able to show that in doses ranging from 0.25 mg. to 0.43 mg. per kilogram of 933 F and three times as much of 1164 F, a purely adrenolytic action was obtained without any

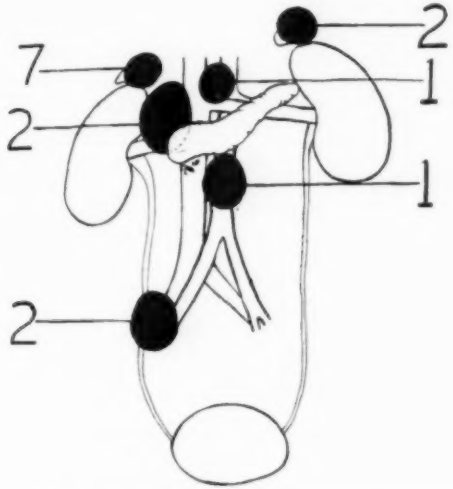

FIG. 11. A drawing showing the location of the pheochromocytomas occurring in the cases at the Presbyterian Hospital, New York City up to 1948, and the number in each situation. Three cases had multiple tumors, two in each case.

sympatholytic effects. After experimental work to show its safety in use, and its effect upon normal subjects, induced hypertensives, and in essential and renal hypertensives, they showed that a significant drop of blood pressure occurred in epinephrine induced hypertensives and in known pheochromocytomas during hypertensive states. They were able to conclude that it was of great aid for the diagnosis of excess circulating epinephrine. The action of these benzodioxanes was rapid and of short duration; the drop in blood pressure following the injection of 20 mg. of 933 F intravenously usually was of 10 to 15 minutes' duration. The use of this drug was described by them and by Cahill [18] in the diagnosis of tumors with persistent hypertension.

The use of dibenamine hydrochloride in pheochromocytoma was reported by Spear and Griswold.[24] This was presented as a diagnostic aid when tumor was suspected and as a therapeutic agent when the diagnosis was confirmed. They were able, in a case with a clinical picture and positive retrograde pyelograms and air infiltration roentgen-ray studies, to block the effects of the pheochromocytoma by the adrenolytic action of dibenamine. Following the administration of 7 mg. per kilogram of body weight, the blood pressure remained normal for 24 hours and the subjective symptoms were relieved for 72 hours. During the period of adrenolytic effect a provocative like histamine had no effect upon the blood pressure, but after the adrenolytic effect was over and histamine again injected, an effect was produced but was less than that seen previously to the administration of the dibenamine.

Precipitation of an Attack of Hypertension in a Resting Stage by an Epinephrine Provocative Such as Histamine

Attacks of hypertension brought about by any mechanism which precipitates a discharge of excess epinephrine in the circulation may be suggestive of a pheochromocytoma. Any causative factor may be used; emotions, fear, anger, change of posture, trauma, massage of the tumor if palpable, cold pressor tests or the direct use of direct chemical provocatives like histamine or mecholyl. Roth and Kvale[25] suggested and used the intravenous injection of 0.05 gm. of histamine base. After a very short initial drop in blood pressure, there was a marked rise associated with symptoms such as precordial and abdominal pain, headache, nausea and diaphoresis. Within six to eight minutes the blood pressure fell from its elevation about 250 mm. Hg to normal. The test on repetition had similar results. Confirmation of the test in pheochromocytoma has been made by Colston,[26] by Spear and Griswold,[24] and others.

In psychoneurotics with hypertensive crises, elevations of blood pressure have been obtained by us with injections of histamine base. These have had a slower rise and were of more sustained type than that seen with tumor. No tumors were found in the psychoneurotics on surgical exploration.

In known pheochromocytomas we did not deem it wise, especially in cases of severe syndromal symptoms, to precipitate attacks with provocatives. In hypertensives from other causes in which we had already obtained a negative benzodioxane reaction, histamine injections were given to produce a crisis if possible as a double check to prevent missing a tumor case. All such histamine injections produced no positive reactions.

The use of mecholyl bromide in doses of 25 mg. subcutaneously has been reported by Guarneri and Evans[27] and has shown a rapid rise in blood pressure, similar to that produced by histamine and with the paroxysmal symptoms and a return to normal in 15 to 20 minutes. The use of this test by Ewart[28] showed that the side reactions of mecholyl may occur with its injection.

LaDue et al.[29] have recently reported that the intravenous injection of tetra-ethyl ammonium salts produces a paroxysmal elevation of the blood pressure in patients with pheochromocytoma and that this rise may be controlled by putting the patient in the upright position.

Roentgenographic Evidence of the Presence of a Tumor Either Within or Without the Adrenal as Shown Without or With Air Insufflation or by Renal Displacement as Shown With Pyelographic Media

The visualization of a tumor is a very important diagnostic procedure in chromaffin tumors. In some cases with a large tumor, a shadow may be present upon plain abdominal films and at times calcification in the tumor if present may bring out its shadow. Not infrequently, pyelography may show displacement of the kidney downward by the tumor mass and in some a flattening of the upper pole of the kidney when the tumor is within the adrenal. In the 18 cases studied by Howard and Barker,[30] 11 had the tumor diagnosed by pyelography. Perirenal insufflation has enabled us to establish the diagnosis when the tumor is within the adrenal.[31] The use of air insufflation in the localization of small tumors of the adrenal must be stressed because the site of such cannot be identified by any other method. Mencher,[32] Bauer and Belt[4] and we[31] have reported upon its value. When the tumor is without the adrenal there is difficulty in outlining it with air and of course recognizing where it is situated. In only one, a right lower ganglia tumor, were we able to show tumor without the adrenal by air insufflation. In several cases in which the tumors were in ganglia near the aorta and the fascial planes under pressure from tumor growth, the failure of air to infiltrate through those fascial planes suggested the site of the tumor.

When the tumor is intrathoracic the tumors have been clearly seen, as reported by Phillips[14] and in the unreported cases of Mayer[33] and Humphreys.[34] Here the lungs conveniently supply the contrasting air and the smooth outlines of these tumors have been clearly shown. Because of the possibility of intrathoracic tumor all cases should have such investigative films.

Treatment

The treatment of pheochromocytoma is surgical removal of the tumor or tumors if more than one can be shown to be present. The operative mortality has shown a progressive reduction. It has been shown that surgical removal of the tumor or tumors completely relieves the patient of all the symptoms and signs of the suprarenal sympathetic syndrome.

A factor in successful operations upon these tumors is the planning of the procedure. If the use of dibenamine will condition the patient so that the danger of handling and releasing a fatal amount of epinephrine will be prevented, a valuable therapeutic aid has been presented. The toxic effects

of dibenamine are by no means negligible, and Hecht and Anderson [35] have noted that sympatholytic effects such as miosis are to be found with the smallest effective doses. In the one case in which we employed small amounts of benzodioxane during operation it was ineffective, but others have observed its value in larger doses in counteracting the cardiovascular effects of operative manipulation of the tumor.

Basal avertin anesthesia appealed to us as offering the anesthesia that would exclude the excitation that other types of anesthetics may cause. Ether and oxygen have been used with the avertin with apparent success.

Children seem to have multiplicity of tumors compared to adults because all of our reported tumors in children (three cases) ultimately had multiple tumors removed. The last case of these developed an asymptomatic tumor in the chest after the functioning tumor in the renal area had been removed. The tumor was discovered accidently on routine chest roentgen-ray and, on removal by Humphreys,[34] was found histologically to be a second pheochromocytoma. This case is the only one on record with the successful removal of an intra-abdominal and intrathoracic tumor. Our other children had abdominal tumors both intra and extra adrenal.

Because of the multiplicity of these tumors and of their growth extension it has been our experience that the best approach to most of these tumors is through the transverse upper abdominal incision. The value of an adequate exposure is obvious and if possible the blood supply to and from the tumor should be occluded before manipulation of the tumor. In large tumors close to the vena cava, protected occlusion clamps may be necessary on the cava above and below the tumor while the vessels of the tumor are manipulated on ligation. The dramatic fluctuations of the blood pressure during operative procedures upon these cases have been reported by many observers.

Subsequent to removal of the tumor the blood pressure may fall to surprisingly low levels. Pre-operative preparation with high salt intake and desoxycorticosterone may be administered as recommended by Biskind, Meyer and Beadner.[36] Norepinephrine in the form of an infusion containing 0.004 gm. of the levo-rotatory or 0.008 gm. of the racemic compound per liter of normal saline should be available as shown by the work of Goldenberg, Apgar and Deterling.[37, 38] Some of these tumors are very vascular and transfusion should be available to replace blood loss. At present the operative risk is less than 16 per cent.

Summary

1. The hormonal tumors of the adrenal medulla have symptoms due to an excess of circulating epinephrine or norepinephrine.

2. The cases vary with the frequency and the amount of the pressor substance secreted.

3. The diagnosis is made by:

(a) History and findings.
(b) Demonstration of excess pressor substance by an antagonist.
(c) Demonstration, if necessary, of the production of excess pressor substance by a provocative.
(d) Demonstration of the presence of a tumor by roentgen-ray.

4. The treatment is operative removal, the danger is during the operation.

5. If the patient survives the operative period, the pressure syndrome is cured and the ultimate prognosis is good because most of the tumors are benign.

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THE PROGNOSIS AND TREATMENT OF HEPATIC INSUFFICIENCY *

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THE term "hepatic insufficiency" may be defined according to the usage of the individual observer of hepatic disease. There would probably be a uniform acceptance of the term for the comatose or disoriented patient with a severe hepatic disorder, such as diffuse necrosis or cirrhosis. This is the way in which the term is most often employed. Probably the majority of observers would agree, however, that it might also be used to apply to more serious clinical states associated with diffuse parenchymal hepatic disease, with jaundice and/or ascites, but without obvious mental depression or aberration. It is doubtful whether anyone would consider the term applicable to such a disease as constitutional hepatic dysfunction or familial non-hemolytic jaundice; although this represents a mild selective form of hepatic insufficiency in which the liver cells are unable to transfer bilirubin to the bile as rapidly as it is formed. It would seem helpful to define the term "hepatic insufficiency" as that state in which the patient's normal economy and activity is seriously interfered with because of a diffuse hepatic injury; in other words, a state in which the functions of the liver are unable to meet the general needs of the individual. This definition is broader than that under which the term is usually employed; nevertheless, it appears to be in best agreement both with etymology and pathologic physiology, and it is therefore the definition which will be employed in the following discussion.

The prognosis and treatment of hepatic insufficiency are alike most difficult to evaluate. They are interdependent in considerable measure, and no attempt at strict separation will be made. Nothing could be more appropriate to this topic than the well known lines from Hippocrates' Book of Prognostics:[1] "He who would know correctly before hand those that will recover and those that will die, and in what cases the disease will be protracted for many days and in what cases for a shorter time, must be able to form a judgment from having made himself acquainted with all the symptoms and estimating their powers in comparison with one another." I am inclined to believe, however, that liver disease must have defied even the keen Hippocratic prognosis, and indeed we must freely admit that our ability to prognosticate or to treat liver disease on any rational basis, has made but tedious and small progress in the intervening centuries.

I will consider first the most important evidence of hepatic insufficiency. One should give due attention to the countenance and the behavior, again, quite in the Hippocratic tradition,[1] "If it be like those of persons in health,

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and more to if like itself, for this is the best of all, whereas the most opposite to it is the worst." A keen watch should be kept for the slightest sign of undue somnolence, disorientation, or euphoria, since these are often the first and ominous harbingers of hepatic coma. With or without these signs there is commonly a manifestation which has been given too little attention and which indeed has been sniffed at too much, and sniffed of too little. This is the "fetor hepaticus," "liver breath," or "amine odor," the perception of which often enables one to recognize hepatic insufficiency, even though jaundice may be slight or absent. Relatively little has been written about this curious odor and still less, practically nothing in fact, with regard to its chemistry; yet it is one of the most faithful indicators of a severely damaged and insufficient liver. One cannot say that it is a deadly sign, except perhaps in those instances where it is so strong as to permeate the entire room and even escape into the hall, attracting the attention of nurses and relatives alike. In these latter, in my experience, death has always soon ensued due to diffuse necrosis or advanced cirrhosis of the liver, more often the former; but it is not uncommon to encounter the odor in fainter concentration, often waxing and waning from time to time, in less severe instances of hepatic insufficiency, cases that may go on to recovery. The sign is seldom observed in patients with jaundice due to extra hepatic biliary obstruction, and then only when there is associated liver damage such as that due to suppurative cholangitis or necrotic metastases. I will not dwell on the other signs often associated with, but not necessarily indicative of hepatic insufficiency, which I am sure are familiar to all of you. I refer to such evidences as palmar erythema, multiple spider-nevi, recent loss of axillary hair, gynecomastia, venous collateral circulation and hemorrhagic tendency, either latent or manifest. I am sure you are aware too that the size of the liver is often of the utmost significance in prognosis. Rapid diminution is well recognized as one of the most ominous signs of all, indicating diffuse necrosis, and as a rule a fatal outcome, although even here exceptions are noted.

If hepatic enlargement is due to fatty metamorphosis or fatty cirrhosis, the prognosis is relatively good; in fact it has become increasingly clear within the recent past, that a good diet alone will frequently serve to induce a remission, and in fact a remission so complete in some instances, that the individual is able to resume a normal life and activity. Before illustrating this effect it will be well to summarize our views as to the important factors in dietary treatment of hepatic insufficiency. The "liver" diet consisting of 150 gm. of protein, 350 gm. of carbohydrate and 100 gm. of fat, is regarded as a minimum daily intake, comprising 2900 calories; it is preferred that supplementary feedings of protein and carbohydrate be taken. The ease with which patients can be induced to eat both the diet and supplementary feedings to a total of 3500 to 4000 calories per day is in itself one of the best indices of prognosis. Rapid improvement may be expected in those who will do this with but little urging and in general the prognosis varies roughly with the appetite, being worse in those with severe anorexia, and, of course, worst in

those who are comatose and will eat nothing. Of crucial importance in all cases with anorexia is the *attention* given to the total food intake from day to day. All too frequently a sense of false security is gained merely by the fact that an adequate diet has been *ordered* or that certain amounts of glucose are being given intravenously, without due inquiry as to whether the 24 hour caloric intake has reached a desirable level. It is best that this be maintained on a *current* basis, not from week to week or even day to day, but from hour to hour. This requires a general awareness of the importance of the problem on the part of the attending physician, house officers, nurses, dietitians, and even the close members of the family, if intelligent and coöperative. It is well that the plan of dietary therapy be discussed at the outset and that frequent additional conferences be held to consider the necessity of changes. Insofar as current maintenance of intake is concerned it is desirable to replace promptly any deficits created by failure to eat the basic 2900 calorie diet as given above. It has been found advantageous in some cases to give small frequent feedings of an enriched * milk mixture on an hourly schedule much as is done with a Sippy regime for ulcer. The total intake may then be calculated at 9 p.m., and if inadequate, may be supplemented during the night either by additional intravenous glucose or drip feeding of the enriched milk mixture through an inlying nasal catheter. The latter should be given slowly, not more than one liter in six hours, and should be withheld in the presence of any tendency to regurgitation.

It is believed of value to administer glucose intravenously in any case of hepatic insufficiency in which anorexia is at all prominent, although the mere giving of intravenous glucose should not create the illusion that everything necessary is being done. From one to two liters of 5 to 10 per cent glucose, the amounts and concentrations commonly employed, provide but 200 to 800 calories, only a small fraction of the actual need. The exact amount and frequency of administration must depend upon individual factors. From one to two liters of 15 to 20 per cent glucose in distilled water, given at a rate of from 0.8 to 1.0 gm. per kilo per hour, provides 150 to 400 gm. of glucose, or 600 to 1600 additional calories. If given at a faster rate a significant loss in the urine must be anticipated. Should insulin be given with the glucose? Proof of its virtue in hepatic insufficiency has not been provided, nevertheless we are inclined to believe that it is beneficial at least in promoting appetite, in certain cases. If mixed directly with the intravenous solution, one unit per 3 or 4 grams of glucose, danger of hypoglycemia is largely removed.

The case described briefly in the following, illustrates the remarkable degree of recovery that may be noted in some instances of "alcoholic" cirrhosis, following a period of abstinence and correction of the dietary deficiency.

* Our experience relates mainly to Meritene provided through the courtesy of the Dietene Corporation of Minneapolis. This is a calcium caseinate-skim milk powder-lactose combination which is readily mixed with milk, one part to six. For purposes of tube feeding the mixture should be prepared wth a malted milk mixer or blender. It should be noted that this mixture produces a tendency to diarrhea in certain individuals.

Case 1. Male, 43, dentist. August 16, 1945: Severe alcoholism, poor diet for many years. Slowly increasing jaundice six months; edema and ascites four weeks. Numerous spider nevi; markedly enlarged liver; palpable spleen. Somnolence; fetor hepaticus. Liver diet; crude liver extracts; B-complex; yeast powder; cholin-cystin. Slow steady improvement first apparent after five weeks in hospital. November 14, 1945, much improved; jaundice slight; no ascites or edema. May 27, 1947, feels entirely well; has resumed work; no jaundice or ascites; liver and spleen not felt; spider nevi have disappeared. February 15, 1948, working and leading a normal life.

The composite liver function studies are shown in figure 1, the histologic changes in the liver in figure 2.

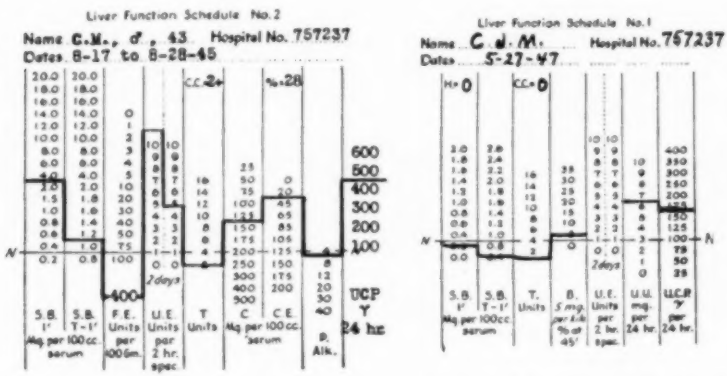
Liver Function Schedule No. 2
Name C.M., ♂, 43 Hospital No. 757237
Dates 8-17 to 8-28-45
Liver Function Schedule No. 1
Name C. M. Hospital No. 757237
Dates 5-27-47
S.B. 1′ Mg. per 100 cc. serum
S.B. T-1′
F.E. Units per 100 Gm.
U.E. Units per 2 hr. spec.
T Units
C Mg. per 100 cc. serum
C.E.
P. Alk.
U.E. Units per 2 hr. spec.
U.U. mg. per 24 hr.
UCP γ per 24 hr.
2 days
N

FIG. 1. Composite liver function studies in case 1. Key: S.B. = serum bilirubin, 1′ = prompt direct, T − 1′ = delayed or indirect, F.E. = feces Ehrlich, U.E. = urine Ehrlich, T = thymol turbidity, C = total cholesterol, CE = cholesterol esters, P. alk. = alkaline phosphatase in Bodansky units, UCP = urinary coproporphyrin, B = bromsulfalein, U.U. = urine urobilinogen, CC = cephalin cholesterol flocculation, H = Harrison test for bilirubin in urine (Barium strip modification), N - - - - N = Upper or lower limit of normal.

From the standpoint of determining the merit of individual therapeutic factors, the above case scarcely represents a controlled experiment; no interpretation is possible as to the relative value of the diet compared with that of the liver extract, vitamin B-complex, yeast powder, or the cholin-cystin mixture. Patek [2] observed similar benefit from the same type of diet plus yeast and B-complex, and more recently, Jones and Volwiler [3] and Buck [4] have reported as much improvement from diet alone.

From the evidence now available, it is believed that the prognosis in cases of so-called "alcoholic" cirrhosis of the above type, is related to the degree of portal fibrosis, bile duct proliferation and adenoma formation with resultant shrinking and distortion of normal liver parenchyma. These changes roughly indicate the extent of previous destruction of liver cells. In other words, the reversibility of hepatic insufficiency as in the above case, would appear to depend upon the remaining amount of liver parenchyma not damaged beyond repair. The remarkable improvement which may occur in spite

of the severe evidence of liver cell injury at the outset, such as in case 1, above, is quite in accord with MacNider's view [5] that the resumption of normal function is due to a return to health on the part of individual cells. There is little doubt that a fatty cirrhosis, in which the enlargement is due mainly to fat rather than to adenomata and connective tissue, offers a much better prognosis than one of the latter type, even though it is still enlarged. The late stage of the disease with marked shrinking and great reduction in functioning hepatic parenchyma is usually beyond help. The simple removal of fat by means of lipotropic agents, is not necessarily attended by improvement, in fact cases have been observed in which a large fatty cirrhotic liver has been observed to diminish steadily under dietary and glucose therapy,

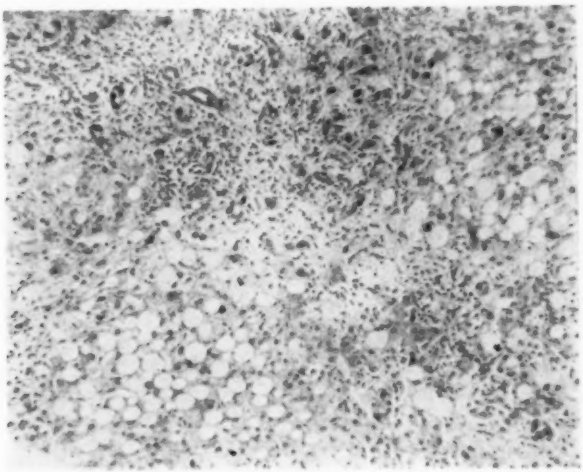

FIG. 2. Histologic appearance of liver biopsy from case 1 (August 20, 1945). Hematoxylin and eosin, × 90.

yet with progressive hepatic insufficiency and at autopsy the finding of an atrophic or typical Laennec cirrhosis. Thus the prognosis probably depends on the amount of relatively normal liver parenchyma remaining at any given time, in other words what is left upon which dietary rehabilitation may be expected to exert a beneficial influence. It is evident, however, that this is not easy to assess. In case 1 the biopsy revealed a histologic picture which did not augur well for the patient's recovery; nevertheless the hepatic insufficiency quite disappeared and the patient is working and feeling well at the present time; in fact there is little doubt that he could pass an insurance examinaton if he were inclined to be untruthful.

At least in the cases of more severe liver disease, prognosis rests on such insecure bases that we cannot deny a period of intensive dietary and glucose

therapy even in instances where the prognosis may appear to be utterly hopeless. The following case clearly illustrates the manner in which one may have to revise the prognosis repeatedly within a relatively short period of time. When first seen it was believed that there was a good chance of improvement in spite of marked jaundice, principally because of the history of faulty diet and alcoholism and because the liver was considerably enlarged. The principal features in this case were as follows:

Case 2. Female, 42. Housewife and tavern operator. Anorexia, vomiting, jaundice six weeks. Poor appetite, low protein diet, considerable alcohol past six years. Spider nevi, ascites, and moderate edema. Liver enlarged and firm; 10 cm. below rib margin in right mid-clavicular line. January 13 to 26, 1948: Liver diet supplemented with enriched milk mixture. No significant improvement. January 26 to February 4, 1948: + 100 gm. salt-poor human albumin daily, total 950 gm. No improvement; somnolent, intermittent fetor hepaticus, increasing edema. February 5 to 28, 1948: 1500 c.c. 20 per cent glucose + 75 units of insulin per day. February 11 to 28, 1948: 10 c.c. intraheptol daily. February 10:—Progressive improvement. Diuresis.

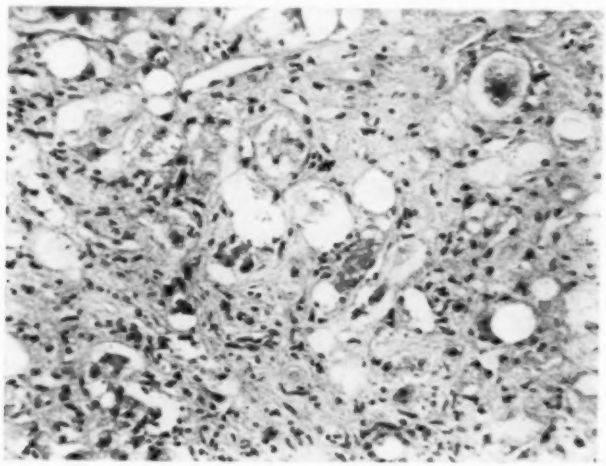

FIG. 3. Histologic appearance of liver biopsy from case 2. Hematoxylin and eosin, × 150.

This case is instructive from a number of standpoints. She failed to improve on a preliminary period of dietary therapy which was believed to be fairly satisfactory, and she appeared to become considerably worse while receiving a large amount of salt poor human albumin. In spite of the fact that her serum albumin rose to a high normal value, there was retention of water rather than diuresis, and with this the patient exhibited increasing evidence of hepatic insufficiency. Liver biopsy done at this time under peritoneoscopic control, revealed a severe fatty cirrhosis with considerable degeneration represented by open spaces (figure 3). The relatively large amount of fat was

rather surprising immediately after the intensive course of human albumin. For a time the prognosis appeared hopeless; yet within a few days after all of the albumin had been given and coincident with the period of intensive glucose and insulin therapy, a striking improvement occurred, jaundice and ascites rapidly abated, and the patient was shortly able to leave the hospital feeling immeasurably better.* This case also illustrates the very real difficulty that is likely to be encountered in attempting to carry out controlled studies of the effect of any one therapeutic factor in patients with hepatic insufficiency. Thus one is frequently persuaded that to continue with a longer trial of but one substance or of one relatively limited therapeutic regime in the face of a worsening clinical state, is to deny the patient the possible benefit of other methods of therapy. In case 2 as just related, it is conceivable that the patient would have recovered slowly but just as well if she had been continued on the simple dietary treatment of the first period on through February 28. While the albumin in this case appeared to do more harm than good the possibility is considered that she might not have had such a favorable result from the large amounts of intravenous glucose, had her nitrogen balance not been favored immediately beforehand. Eckhardt and co-workers [6] have shown that human albumin given intravenously is metabolized rather completely giving rise to a markedly positive nitrogen balance; at the same time they found a lag of several days from the time of injection to the peak effect on metabolism. Thorn and his associates,[7] and more recently Patek and co-workers,[8] have shown quite clearly that salt poor albumin administered intravenously in patients with cirrhosis and ascites, is lost in considerable amount into the ascitic fluid. They are inclined to believe that this may be the principal reason why the material is so little effective; yet it does not adequately explain the lack of diuresis and the marked weight gain with increasing signs of hepatic insufficiency, in spite of an elevation of the serum albumin to 5.0 per cent, such as occurred in case 2. This rather paradoxical situation, which has been observed in other cases of cirrhosis as well, and has been discussed in more detail in a separate communication,[26] simply emphasizes our need of more information regarding water balance in liver disease.

It is doubtful that the intraheptol played any significant rôle in the diuresis and ensuing improvement which commenced prior to its administration in case 2.

Case 3, the salient features of which are given in the following, is of particular interest in that, while the patient's initial status did not appear to be as grave as either of the first two cases, there was no response to dietary, intraheptol, or methionine therapy.

Case 3. Male, 54. Contractor. October 2, 1946: Long-standing chronic alcoholism until three months ago; no history of dietary deficiency although meat intake has always been rather small. Jaundice, ascites. Liver markedly enlarged. Numerous

* Seen again on May 25, 1948, she was feeling very well and the jaundice had now quite disappeared. This status was maintained as of August 15, 1949.

spider nevi. Liver diet, low sodium, plus B-complex capsules. October 23, 1946: Intraheptol commenced: 10 c.c. 3 × weekly intravenously. November 26, 1946: No improvement, liver enlargement about as before. Edema persists. Intraheptol discontinued. Liver diet, low sodium, plus vitamin B-complex, continued. April 10, 1947: Condition unimproved; increasing somnolence. Methionine gm. II q.i.d. for one day followed by confusion. April 17, 1947: Persistent jaundice and ascites. Frequently disoriented or unconscious, episodes repeatedly precipitated by methionine, at times spontaneous. Macrocytic hemolytic anemia; marked hematinemia. 100 gm. salt poor human albumin in 24 hrs., without obvious effect. April 30, 1947: Death. Necropsy: Liver wt. 1240 gm., advanced portal cirrhosis; very little fat.

Representative composite liver function studies in case 3 are shown in figure 4. It is impossible to determine what factors underlay the lack of response in this case. He ate well, and so far as could be determined, abstained completely from alcohol during the last two years of his life. No improvement in appetite was noted following long continued use of intraheptol.

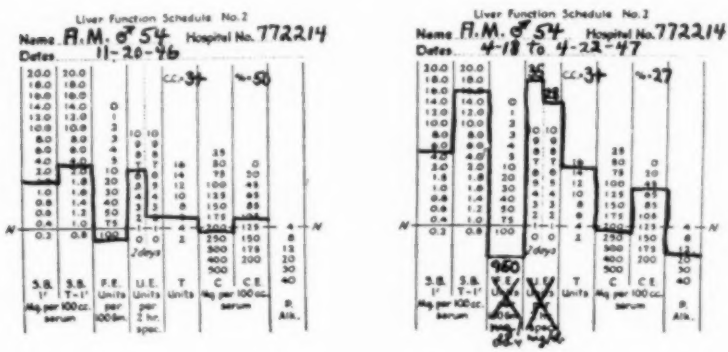
Liver Function Schedule No. 2
Name A.M. ♂ 54 Hospital No. 772214
Dates 11-20-46
Liver Function Schedule No. 2
Name A.M. ♂ 54 Hospital No. 772214
Dates 4-18 to 4-22-47

FIG. 4. Composite liver function studies in case 3 (for key see caption to figure 1).

Methionine was not given until rather late in the patient's illness, although he was still ambulatory at the time that it commenced. It was only given for short periods, due to the fact that the patient repeatedly became somnolent and semi-comatose after its administration. It was clear, however, that there were other factors in addition to methionine, in precipitating these episodes; the patient's wife related that on several other occasions he had become somnolent to the point where she could not arouse him. Case 3 developed another interesting phenomenon which appears to have ominous significance; namely, an outspoken, macrocytic hemolytic anemia with hematinemia. The occurrence and significance of hematinemia in liver disease has been commented on by a number of observers, [9, 10, 11, 12] and has been considered in some detail elsewhere. [13, 14] While in general the appearance of an acute macrocytic hemolytic anemia with hematinemia may be regarded as a very untoward prognostic sign, it is not incompatible with recovery, and occa-

sional instances have been noted in which marked improvement has occurred after transitory episodes of this type.

In case 4, also an example of alcoholic cirrhosis, the factors of infection and secondary malnutrition in precipitating hepatic insufficiency appeared to be prominent. This case was described in a previous communication. [15]

Case 4. Male, 58. Chronic alcoholism; moderate obesity. September 22, 1941: Admitted in semi-stuporous state. Disoriented. Mild jaundice. Fetor hepaticus. Right saphenous thrombophlebitis. Temperature 102.4° F. Blood culture negative. Markedly enlarged liver and spleen. No ascites. Urine urobilinogen:

9–26	9–27	10–1	10–12	10–16	10–22	12–29
++++	++++	82.1 mg.	67.0 mg.	++	++(34 mg.)	+++

Serum bilirubin: I′ = 0.7; T = 1.48 (September 27, 1941). Serum proteins: T = 5.8; A = 2.7; G = 3.1 (September 27, 1941). September 23 to 26: Fluids, glucose, fruit juices. *No protein or vitamins. Marked improvement;* oriented; appetite returning. September 26 to October 25: P 150, C 200, F 30. Yeast, liver extract, vitamins. Discharged in relatively good condition.

The above instance simply illustrates the difficulty in evaluating therapeutic measures or substances supposed to have peculiar merit in the treatment of hepatic insufficiency; since it is evident that the hepatic coma promptly disappeared with bed-rest, fluids, and glucose alone. The main improvement had occurred before the patient was given any proteins or other accessory food substances. Although a biopsy was not secured in this case, it may be assumed from the rapidity of his response and progressive improvement, that the liver was largely fatty and only mildly cirrhotic. In passing, the rather striking dissociation of impairment of liver functions may be remarked upon. The urine contained large amounts of urobilinogen but the serum bilirubin was only slightly elevated.

As between the fatty and non-fatty types of "hypertrophic" cirrhosis (using the term hypertrophic in the broad sense) the former quite clearly has the better prognosis, and as we have seen in the foregoing cases, striking improvement may occur even though extensive fibrosis and change in the hepatic architecture has taken place. In the cirrhosis and diffuse hepatic injuries which are primarily non-fatty and non-dietary in genesis, it is doubtful that dietary therapy is of nearly as great significance in prognosis or treatment. In fact the more one studies this group, the more one is inclined to the belief that the physician's principal rôle is that of protecting the patient against further insult such as may arise from exertion, fatigue, malnutrition or negative nitrogen balance, drugs or chemicals, anesthesia, or needless cholecystectomy or exploration of the common bile duct. Of the utmost importance in this regard is an awareness of the possibility of diffuse liver disease such as hepatitis or cirrhosis in the patient whose past history of colic or of known gall stones or biliary tract disease, suggests an extra- rather than an intra-hepatic cause of jaundice. Case 5 is illustrative of such a pitfall.

Case 5. Male, 59. October, 1944: Cholecystectomy. Pooled plasma given on first post-operative day because of moderate decline in blood pressure. Uneventful recovery from the operation. February, 1945: Jaundice, pruritus. The patient was advised elsewhere to adhere strictly to a milk diet and to take atropin and nitroglycerin. Continued activity was allowed. February 25, 1945: Admitted to a private hospital in Minneapolis. Deep jaundice, examination otherwise negative. Serum bilirubin 39 mg. per cent, prompt direct van den Bergh. Urine Ehrlich test +. March 9, 1945: Surgical exploration (diagnosis common duct stone). Normal appearing common duct and cholangiogram. Progressive deterioration; hiccough, evisceration, bloody stools, stupor, fetor hepaticus. March 23, 1945: Death. Liver weight 1425 gm. Widespread central necrosis.

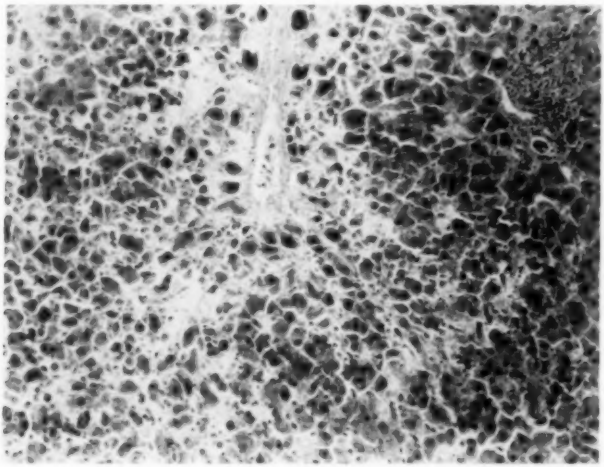

FIG. 5. Histologic appearance of liver of necropsy in case 5. Hematoxylin and eosin, × 90.

The histologic appearance of the liver is shown in figure 5.

What measures might have been taken to avoid the tragic outcome in the above instance? An examination of the record in this case revealed that the plasma which was given on the first postoperative day perhaps represented an overzealous attitude toward a moderate decline in the blood pressure. It has become increasingly clear that transfusion, especially of pooled plasma, should not be employed without a very real indication. The risk of homologous serum jaundice from the use of pooled plasma must be reckoned as between 5 and 10 per cent.[16, 17] This of course deters one from using it in the treatment of hepatic insufficiency, although the experience gained during the recent war indicated that it may be of considerable value in helping to tide over the more severely ill patients.[18] The author is acquainted with one instance in which pooled plasma was used with apparent benefit in treating a severe hepatic insufficiency due to spontaneous (epidemic) infectious

hepatitis. The patient recovered but approximately four months later became jaundiced again and this time succumbed to a diffuse hepatic necrosis which may well have been on the basis of homologous serum hepatitis acquired from the plasma given four months earlier.

At the time that the above described case 5 developed what was in all likelihood homologous serum jaundice, the final outcome still might have been avoided had he been put promptly to bed on a good diet instead of which he was allowed continued activity on a restricted diet and given drugs which were obviously intended to relieve an extrahepatic biliary obstruction. Later, when he was admitted to the hospital, a composite liver function study might well have indicated the gravity of his disease. There was marked hyperbilirubinemia and on one occasion the qualitative urine urobilinogen test was positive, but additional studies were not carried out. A careful investigation of the cholesterol and cholesterol esters, and of the qualitative and quantitative aspects of the serum proteins would have been very helpful, and if doubt had still existed a liver biopsy would have been less compromising than an exploration of the common duct under general anesthesia. This patient received methionine in considerable amounts postoperatively, together with glucose, amino acids, and repeated infusions of plasma, all to no avail.

In case 6, which is described in the following, the composite liver function study gave warning of a considerable degree of hepatic insufficiency. This patient, a housewife 30 years of age, had had a cholecystectomy in July 1946. Following the operation she had a wound abscess and was quite ill with considerable fever for a period of two weeks, during which she was given three blood transfusions from individual donors. At the end of this time the abscess was drained and the patient recovered uneventfully. Approximately three months later she became jaundiced again, without pain or fever, and the jaundice deepened progressively. It was believed that she had a common duct calculus and she was referred to the University Hospital for choledochostomy. Physical examination revealed a rather deep jaundice, the nutrition being quite well maintained. The patient was alert and intelligent and in no distress. Her appetite was fairly good. Fetor hepaticus was observed. The liver was palpable coming down about 3 cm. below the right costal margin in the mid-clavicular line. The spleen was not palpable. There was no edema or ascites. A composite liver function study is shown in figure 6. This profile was much more suggestive of a diffuse parenchymatous jaundice than a common duct stone, and operation was consequently deferred. The patient was treated conservatively with a "liver diet," but at the end of two weeks the jaundice had not subsided and liver biopsy was therefore determined upon. The liver was not large enough to warrant a direct, subcostal biopsy. Peritoneoscopy was not considered because of the probability of multiple adhesions secondary to the previous operation and wound abscess; therefore, at our request, Dr. Richard Varco made a small incision in the right upper quadrant under local anesthesia, visualized and palpated the liver and took a 1 cm. wedge for microscopic examination. This revealed the

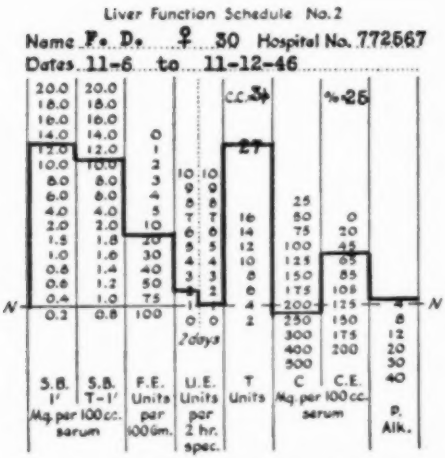

FIG. 6. Composite liver function study in case 6 (for key see caption to figure 1).

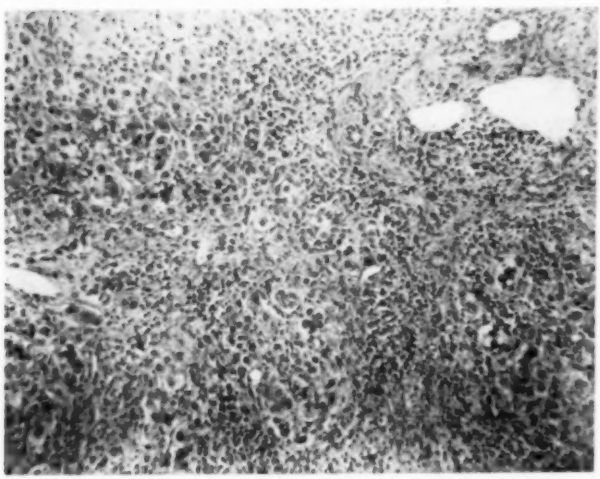

FIG. 7. Histologic appearance of liver biopsy from case 6. Hematoxylin and eosin, × 90.

picture shown in figures 7 and 8, a much more extensive diffuse liver disease than had been anticipated. The cirrhosis is not as apparent with hematoxylin and eosin (figure 7) as it is when the section is stained with Mallory's connective tissue stain (figure 8). It was believed that this patient was suffering from homologous serum hepatitis and early cirrhosis. With further

bed rest and maintenance of caloric intake, she gradually improved and her jaundice slowly diminished. She was able to return home and has since resumed some of her activity, although she reports by letter that the jaundice has not entirely disappeared. It seems likely that this patient will have a permanent residual cirrhosis. It is believed that another operation in this case, in the face of the evidence of the liver damage noted in figures 7 and 8, would have invited disaster. The patient's prognosis is sufficiently serious as it is, but at least she is alive and much better than at the time of admission.

From the standpoint of improving the prognosis by avoidance of needless operations, one of the most well concealed pitfalls is the case of diffuse cirrhosis with mild jaundice who presents because of "pseudo" gall stone colics.

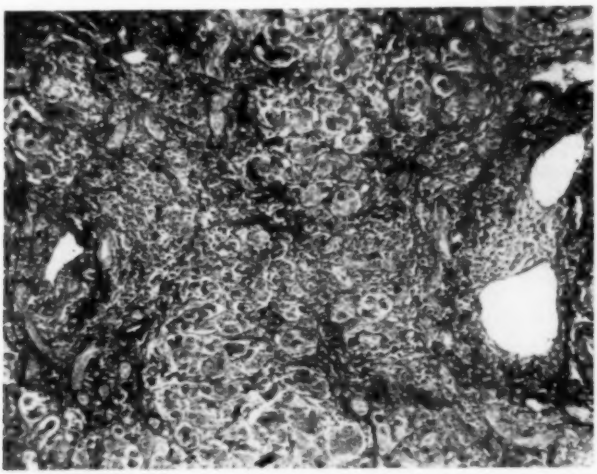

FIG. 8. Histologic appearance of liver biopsy from case 6. Mallory's connective tissue stain, × 90.

This situation was well described many years ago by Naunyn [19] who recognized that typical biliary colics occurred in some non-calculous cases of cirrhosis. Our own experience includes at least half a dozen such instances the majority of which have had choledochostomy, fortunately without great harm, but also without benefit. In these the diagnosis of cirrhosis was not suspected preoperatively. It is possible that the composite liver function study will serve in the future, to put one on guard in such instances and that the method of cholangiography under peritoneoscopic control,* [20, 21] may then

* Since this was written we have attempted this method repeatedly, but with little success mainly due to difficulty in needling the gall-bladder. At present we prefer a small laparotomy under *local* anesthesia. This usually permits cholangiography on the table, as well as direct visualization of the liver and liver biopsy. If morphine and barbiturates are avoided the procedure is well tolerated and does not compromise the patient, unlike a choledochostomy.

reveal the status of the common duct sufficiently well that exploration may be avoided.

Case 7 illustrates the very treacherous nature of hepatitis, and emphasizes again the difficulties of prognosis. In this instance the outcome was disastrous in spite of a relatively conservative regime. The patient, a housewife of 55, was first seen in consultation in another hospital, in April, 1947. At this time she had been jaundiced for about six weeks, the jaundice first appearing after a brief attack of relatively mild diarrhea, experienced while she was on a vacation trip in the south. She was in another hospital in Minne-

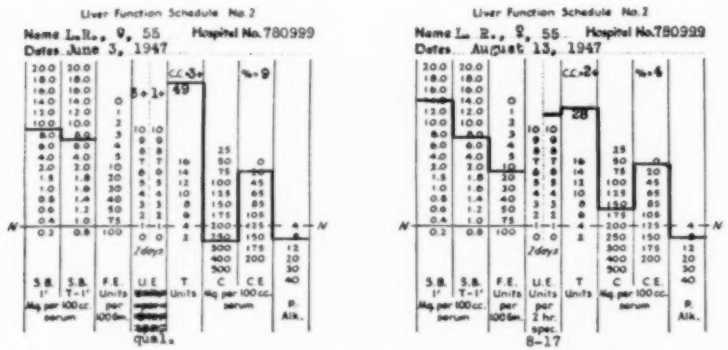
Liver Function Schedule No. 2
Name L. R., 9, 55 Hospital No. 780999
Dates June 3, 1947
Liver Function Schedule No. 2
Name L. R., 9, 55 Hospital No. 780999
Dates August 13, 1947

FIG. 9. Composite liver function studies in case 7 (for key see caption to figure 1).

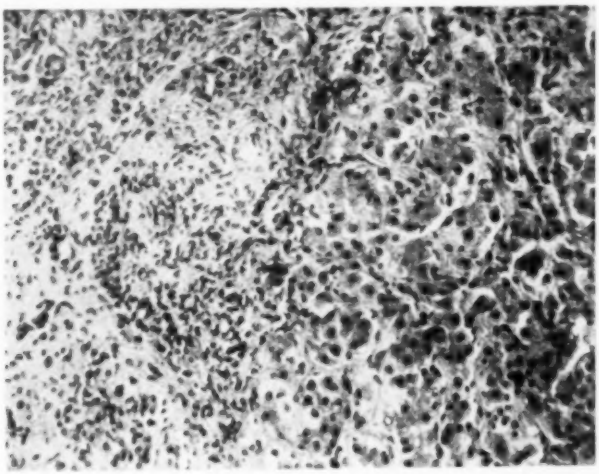

FIG. 10. Histologic appearance of liver biopsy in case 7. Hematoxylin and eosin, × 150.

apolis for a two month period, from April to June, 1947. Her jaundice gradually lessened, and she left the hospital about the middle of June considerably improved, although with distinct residual jaundice. During July 1947 she was up and about doing most of her own housework. On August 1 the jaundice deepened, the patient lost strength and appetite and was admitted to the University Hospital. In spite of the fact that the composite liver function studies (figure 9) strongly indicated a diffuse disease of the liver, either hepatitis or cirrhosis, or both, the question was raised as to the possibility of a common duct calculus or cancer, and in order to exclude this a peritoneoscopy and liver biopsy was done. The histologic appearance is noted in figure 10. The procedure appeared to be well tolerated, but about 36

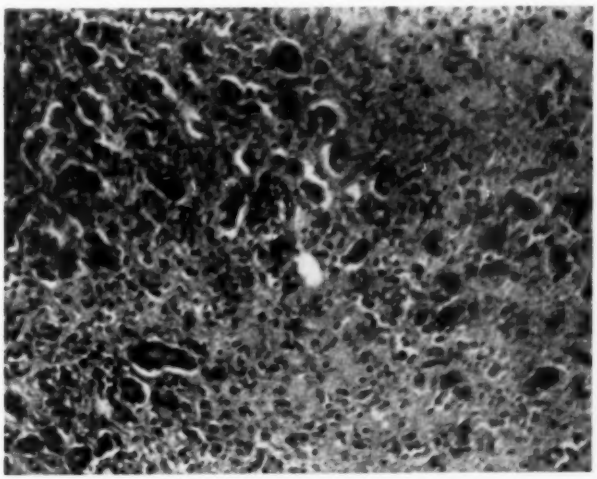

FIG. 11. Histologic appearance of liver obtained at necropsy in case 7. Hematoxylin and eosin, × 150.

hours later the patient became disoriented and within another 12 hours was comatose. In spite of intensive therapy which included continuous drip feeding, large amounts of glucose, and 150 gm. of salt poor human albumin intravenously during a two day period, the course was rapidly downward. The liver dullness disappeared and the fetor hepaticus was outspoken. There was some ascites and increasing edema. At necropsy the liver weighed 1050 gm., and microscopically revealed extensive necrosis (figure 11) which had not been observed in the biopsy taken four days before death (figure 10). The brain showed areas of perivascular demyelinization and endothelial proliferation, findings * which are commonly encountered in patients dying of hepatic

* Personal communication from Dr. A. B. Baker, Professor of Neurology, University of Minnesota.

coma, and which may well be taken as representing evidence of "hepatic encephalopathy."

The relationship of the peritoneoscopy and liver biopsy to the development of fatal hepatic insufficiency in this case is problematical. It should be noted that morphine sulfate gr. ¼ (0.016 gm.) was given just prior to the procedure. This was unfortunate since it is well recognized that morphine is not without danger in the presence of hepatic insufficiency [22]; yet the importance of this factor is questionable because of the 36 hour interval during which there was no evidence of deterioration. It is not unlikely that a reduction in food intake incident to the procedure may have been at least equally important. In retrospect the composite liver function study gave warning of the precarious state of this patient's liver and was perhaps sufficient to contraindicate even the peritoneoscopy and liver biopsy. Two points in particular deserve emphasis in the functional profile of August 13 (figure 9). The first is the relatively large amount of urobilinogen in the urine in the presence of a high grade exclusion of bile from the intestine; the second, the unusually low percentage of cholesterol esters; our experience indicates more and more that values below 15 and especially below 10 per cent are of grave prognostic import, although not incompatible with recovery.

Case 8 illustrates again the remarkably rapid improvement which may occur in cases of severe hepatic insufficiency; and again the difficulty in evaluation of therapy:

Case 8. Male, 64. May 1947: Nephrectomy; sarcoma of mesonephric ridge. Many blood transfusions before, during and after operation. October 10, 1947: Anorexia, nausea. October 17, 1947: Jaundice, pruritus, light stools, dark urine. October 24, 1947: Deepening jaundice, enlarged liver and palpable spleen; marked fetor hepaticus. October 24, 1947: Liver diet. October 27, 1947: + 300 gm. glucose daily, by mouth. October 29, 1947: + 100 gm. glucose i.v. daily. November 7, 1947: Condition worse; deepening jaundice; marked fetor hepaticus; lethargic and restless; liver has diminished in size. November 7 to 12, incl.: 100 gm. salt poor human albumin daily intravenously (600 gm. total). November 10 to 21, incl.: Progressive improvement. November 21: Discharged feeling quite well; jaundice fading. January 6, 1948: Condition good, no jaundice.

At first glance it appeared that the effect of the albumin in this case was little short of miraculous; judging from the patient's behavior and appetite no improvement was apparent until three days after the first administration of albumin. The attending physician was quite convinced of its beneficial effect; nevertheless it was noted that just before the first albumin the serum bilirubin value was already somewhat reduced being 38 mg. on November 6 as compared with 49 mg. on November 5. Thus the question is raised as to whether a spontaneous improvement had not commenced just prior to the albumin therapy. In any event it is clear that further studies are needed of the effect of albumin in various types of diffuse hepatic injury with hepatic insufficiency.* At the same time it must be appreciated that the administra-

* Since this was written a considerable further experience with salt poor human albumin in cases of hepatitis and cirrhosis has failed to provide definite evidence of beneficial effect.

tion of albumin is not without some danger from the standpoint of increasing the blood volume, embarrassing the myocardium, and producing pulmonary edema. Our experience in this regard has been reported in a separate communication.[28]

The dissociation of functional disturbance in cases of hepatic insufficiency is of much interest and deserves further comment. Fatal hepatic coma with little or no jaundice is not often observed but has been sufficiently well documented.[23, a, b, c, d] The following case is illustrative.

Case 9. Female, 69, housewife. Intermittent peptic ulcer symptoms for 40 years. Vomiting, hematemesis, melena for four days prior to hospital admission. Disorientation from fourth hospital day. Coma for last four days of life (fifth to ninth hospital days). Questionable slight jaundice on last day. No other significant findings. Composite liver function study as seen in figure 12. Necropsy: Advanced portal cirrhosis, liver wt. 1150 gm.; bleeding esophageal varices; benign chronic gastric and duodenal ulcers.

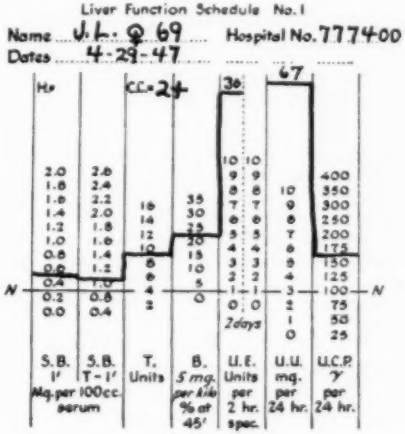

FIG. 12. Composite liver function study in case 9 (for key see caption to figure 1).

The large amounts of urobilinogen in the urine in case 9 indicated that bile was entering the intestine and by contrast with the serum bilirubin, that the liver excretory function for bilirubin was hardly impaired. This situation may be compared with the more usual one in severe hepatic insufficiency, i.e., that of marked hyper-bilirubinemia with a preponderance of 1′ or prompt reacting serum bilirubin. This is of special interest with relation to the concept that the liver cells convert the delayed or indirect reacting bilirubin (globin) to the prompt reacting sodium bilirubinate and that the presence of the latter in the blood is an evidence of regurgitation of bile.[24] The finding of 30 or 40 mg. of prompt reacting bilirubin per 100 c.c. of blood shortly

before death in a case in which diffuse necrosis of the liver is found, poses the question as to how this may be if its formation is in reality a function of the liver cell. As a matter of fact the same question may be raised with respect to the urea nitrogen. It is not particularly uncommon to observe marked elevations of prompt reacting serum bilirubin and of urea nitrogen just before death in cases of subacute diffuse hepatic necrosis, or cirrhosis. Perhaps the most logical theory to explain these increases is that the necessary enzyme systems are still available in the liver in spite of its histological appearance. Another possibility is that the v. Kupffer cells are more important than the polygonal cells in bringing about this conversion, and that they have retained greater functional integrity. While this matter is thus of considerable fundamental interest it is pertinent to the present topic only to the extent that elevations of these substances, even though their formation may depend on hepatocellular function, nevertheless cannot be construed favorably from a prognostic standpoint.

This discussion will have served, I hope, to emphasize some of the difficulties in the prognosis and treatment of hepatic disease, difficulties which are inherent because of the multiplicity of the functions of the liver, the remarkably variable dissociation of functional impairment encountered in disease, and the liver's ability to regenerate in spite of severe injury. Perhaps too this discussion will have served to emphasize that protection of the injured liver against further insult is the main responsibility of the physician. Left quietly to itself with complete rest and adequate nutrition even the badly damaged liver is often able to lick its wounds and become sufficient, but it may turn to the wall if discouraged by fatigue, malnutrition, chemicals, or trauma. As Adamson [25] has pointed out, it is indeed curious that the great anatomist, Bartholin, upon discovery of the lacteals, playfully wrote an epitaph for the liver in which he relegated it to the rôle of a "large dull bile producer," rather than "maximus heroibus" as Galen would have had it. On this score at least, it appears that Galen's intuition did not lead him astray.

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PREFRONTAL OPERATIONS FOR THE TREATMENT OF MENTAL ILLNESS*

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Prefrontal operations for the treatment of mental illness may be divided into two main classes: 1. those involving interruption of the white matter (lobotomy or leucotomy); 2. those involving resection of cortical gray matter (subtotal cortical ablation; frontal gyrectomy; topectomy).

The first effort to treat psychotic patients by surgery upon the brain was made by Burckhardt of Switzerland in 1891, who reported some degree of improvement following unilateral cortical ablations.[1] Then in 1937, Moniz of Portugal [2] reported encouraging results following bilateral prefrontal leucotomy, a procedure devised and developed by him, and later modified by Freeman and Watts who introduced it to North America as prefrontal lobotomy.[3]

Lobotomy or leucotomy, which interrupts fibers in the white matter of each frontal lobe, was originally done through a small trephine opening by a special instrument called a leucotome.[2] Many neurosurgeons today, however, prefer to divide the white matter with the aid of a small suction apparatus and the electro-cautery, under direct vision through a reasonably large opening in the skull.[4, 5, 6] In the standard operation of Freeman and Watts [3] the white matter is divided bilaterally just anterior to the plane of the coronal suture; in their radical lobotomy sometimes carried out as much as 12 mm. posterior to the coronal suture, a greater amount of each frontal lobe is disconnected and consequently profound and permanent personality defects may ensue. This risk is minimized if less radical lobotomies are done, such as the various types described by Freeman and Watts,[3] Hofstetter et al.,[7] Van Wagenen,[8] Schwartz [9] and others. Influenced in part by some of the work on topectomy,[10, 11, 12] Scoville recently has achieved encouraging results in psychotic patients by undercutting the gray matter bilaterally in different parts of the frontal lobes.[13] Another recent development is Freeman's transorbital lobotomy,[14] a procedure that sacrifices a relatively small amount of white matter. While at one time transorbital lobotomies were done with sterile ice-picks, currently a small spatula-like leucotome is used, which is inserted above the eyeball beneath the upper lid, and is then tapped through the orbital plate into first one and then the other frontal lobe. White matter is then partially divided by manipulating the inserted leucotome transversely at depths of 4 and then 7 cm. Apparently the transorbital

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technic is not as effective for certain advanced psychotic states such as chronic schizophrenia as it is for depressions, obsessive-compulsive neuroses and other anxiety states. Freeman feels that this procedure is apt to be more effective when carried out under electric shock narcosis, instead of general anesthesia, and then followed by a course of electric shock treatments.

Brain operations for the relief of mental illnesses are not effective unless carried out in the frontal lobes, judging from unsuccessful results following occipital,[15] temporal,[16] and parietal lobotomies.[17] Moreover, experiences with cortical ablations involving subtotal removal of the cingulate gyri or the ventral surface [12] suggest that removal of these portions of the frontal lobes is not necessarily as important in the surgical improvement of mental disturbances as disconnection or removal of cortex in the region of areas 9, 10 and 46 of Brodmann. This is of interest in view of the work of Walker,[18] Legros Clark [19] and others, showing that areas 9, 10 and 46 are important stations for thalamic projections from the dorso-medial thalamic nuclei, and fits in with the theory that thalamo-cortical circuits may be of major importance in the manifestations and control of emotion or "affect." Interruption of these circuits is believed to benefit mental disturbances principally by reducing anxiety, tension and excess emotional charge. Such interruption may be accomplished at the cortical level by ablation (topectomy, gyrectomy); at the subcortical level by dividing white matter (various types of lobotomy); or at still deeper levels by destroying parts of the thalamic nuclei (thalamotomy).[20]

Experience with the various procedures just mentioned suggests that two factors are important in securing beneficial effects. One is quantitative; the degree or amount of nerve pathways interrupted must be *sufficient*. The second factor is qualitative: that is, the anatomical site of the lesion is important.

Cortical Ablation: As mentioned above, the first efforts to treat psychotic patients by cortical ablations were reported by Burckhardt in 1891.[1] In 1946, Heath and Pool [10] decided that limited cortical ablations confined to the prefrontal region of the brain might prove more specific and more satisfactory than prefrontal lobotomy, which up to that time had sometimes seemed a rather blind and uncertain procedure too often followed by unfortunate side-effects. Accordingly, a small series of subtotal ablations of cortex from the frontal lobes of psychotic patients was done [10] which later led to an extensive study of various types of cortical ablation conducted by the Columbia-Greystone Associates early in 1947.[12] This coöperative venture, together with further study by Pool, Heath and Weber,[21, 22] eventuated in the more or less standardized type of cortical ablation, *topectomy* (described below) which in turn closely resembles one type of cortical ablation (frontal gyrectomy) reported by Penfield in 1947.[23]

Topectomy (from topos, place; ektos, a cutting out) as currently practised is a topical type of cortical ablation limited to the rostromedial portion of each frontal lobe, as this seems to be an effective region for removal in

this type of operation. Operations are bilateral because it has been shown (a) that behavior changes in the laboratory animal are usually not lasting or significant unless cortical ablations are bilateral [24]; and (b) because prefrontal lobotomies (except for relief from some kinds of pain) [25] are not effective unless carried out bilaterally.

The topectomy operation is usually done under general anesthesia. After a coronal scalp incision within the hair line has been made, a bifrontal bone flap is turned. The dura is then opened bilaterally so that a block of tissue extending no deeper than the gray matter can be resected from each frontal lobe. Each resection is begun approximately 2.0 to 2.5 cm. in front of the coronal suture at the midline, and extends thence 5.5 cm. to 6.0 cm. anteriorly, 3.5 to 4.0 cm. laterally, and no more than 1.9 to 2.0 cm. in depth. The adjacent medial aspect of the frontal cortex is included in the resected blocks.

While the topectomy operation sometimes requires more time than a lobotomy (two to three and one-half hours), topectomy sacrifices far less frontal lobe function than does the usual prefrontal lobotomy and, therefore, very rarely results in unfortunate post-operative effects such as permanent incontinence and profound blunting of the personality.

Complications: Post-operative complications after topectomy consist of a 16 per cent incidence of occasional convulsive seizures (always controlled by appropriate medication); a rare post-operative hematoma (treated successfully by re-operation); and temporary urinary incontinence in some cases. Permanent incontinence may occur after a radical prefrontal lobotomy but is not apt to follow the other types of operations described.

The mortality rate after prefrontal lobotomy is 1.5 per cent [3] to 6 per cent [26]; after transorbital lobotomy, less than 1 per cent; after topectomy (author's series of more than 100 cases), 0.

Selection of Patients: As a general rule none of these procedures should be considered until an adequate trial of psychotherapy and shock therapy has first been carried out and found wanting, and unless the patient has been seriously ill for at least two years. Every effort should then be made to select cases carefully and to select the most conservative type of operative procedure for each individual case, as a more radical procedure can always be done later if necessary. The most conservative procedure as to the amount of brain tissue sacrificed is transorbital lobotomy; the next most conservative and simple procedure is the undercutting type of lobotomy described by Scoville [13]; while next in order comes topectomy. A full scale standard prefrontal lobotomy or leucotomy sacrifices more frontal lobe connections than does any of the other procedures just listed and in the opinion of the author is, therefore, more radical and hence should be considered only as a last resort.

The categories of mental illness chosen for psychosurgery [3, 5, 6, 11, 21, 22] include schizophrenia (dementia praecox); obsessive-compulsive neuroses; manic-depressive psychoses; involutional, reactive, or agitated depressions;

other conditions leading to severe anxiety; or depressed states with a suicidal trend. By far the largest group operated upon, because one of the most difficult to treat by any means, is the schizophrenic.

A psychiatrist, of course, must always select the cases for surgery and share not only in the choice of operative procedures but in the post-operative care.

Results: Really good results in the schizophrenic group following prefrontal lobotomy [6] or topectomy [21, 22] are obtained in about 20 per cent of the cases; fairly good results in another 20 per cent or more; and insignificant or poor results in the remainder. Most cases in the obsessive-compulsive group and the involutional type of depression are greatly improved by these procedures, while the psychopathic personality is least apt to be improved.

In the schizophrenic group the paranoid patient between the ages of 27 and 45 with at least some preservation of "drive" and will-to-get-better is most apt to improve. Results in manic-depressive or agitated and reactive depressive cases are, as a rule, less consistently good.

In summary, it appears that while we are apparently approaching a position where specific surgical procedures upon the brain may be selected for the relief of specific mental or emotional disturbances, much investigative work must be done before we can hope fully to understand the mechanisms and perfect the treatment of mental illness.

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STUDIES ON THE CORONARY CIRCULATION. VI. LOSS OF MYOCARDIAL CONTRACTILITY AFTER CORONARY ARTERY OCCLUSION *

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Introduction

It is well known clinically and experimentally that an ischemic portion of myocardium may bulge or "balloon" out during systole.[1] This remarkable phenomenon, which is of diagnostic and physiologic importance, has been very difficult to study in the past. Clinically, it has been observed on patients under the fluoroscope and may be graphically recorded by the electrokymogram and roentgenkymogram.[2-8] The information that can be obtained by such clinical procedures is relatively limited. At best, these clinical methods can tell us only whether bulging in systole is or is not present. It is highly probable that slight degrees of bulging may be overlooked altogether; and it has been reported that non-contractile regions may indeed be found in normal hearts.[9]

There have been great difficulties in studying this phenomenon in the experimental animal. This is because the heart beats so rapidly and the region of ballooning is so small that by ordinary observation it is difficult to be sure whether or not this phenomenon is present. The only systematic effort to study loss of myocardial contractility which we could find is the excellent work conducted by Tenant and Wiggers.[1] By means of a mechanical device placed over the bulging myocardium of the dog's heart, they recorded its motions and observed that the ischemic region ceases to contract within one minute after coronary artery occlusion.

It has been generally assumed that this loss of contractility of the ischemic myocardium is due to the accumulation of metabolites which prevent further contraction, analogous to the loss of function of a limb completely deprived of its blood supply.[10] This assumption is generally based on the erroneous idea that the coronary arteries are end arteries and that following coronary artery occlusion the ischemic myocardium is completely devoid of blood supply. In a series of experiments from this laboratory,[11-14] it has been demonstrated that the coronary arteries are not end arteries. Intercoronary anastomoses up to 200 micra in diameter have been found and shown to perform many vital functions [13]:

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(1) The nourishment and strengthening of the ischemic myocardium, thereby preventing rupture and aneurysmal dilatation of the myocardial wall.
(2) The promotion of healing of infarcted heart muscle.
(3) The determination of the size, shape, and location of the resultant infarct.

Accepting as fact the *non-terminal* nature of the coronary arteries, we decided to reinvestigate this problem of non-contractility of ischemic myocardium.

We have studied this phenomenon in the exposed beating hearts of dogs by means of slow motion pictures. There are many advantages to this technic:

(1) The heart is greatly magnified, which reveals finer detail.
(2) The heart's motion is slowed.
(3) Repeated observations are possible.

It is apparent that for the purpose of this study the method of slow motion pictures is ideal and is much superior to the mechanical method of Tenant and Wiggers referred to above or to the various roentgen-ray methods employed in man.

Part I. Observations on the Loss of Contractility of Ischemic Myocardium

Method: In 30 anesthetized dogs, as described elsewhere,[13] the heart was exposed and the anterior descending branch of the left coronary artery was ligated. Colored motion pictures of the beating heart *in situ* were made at 48 to 100 frames per second before, during, and after coronary ligation. Further details of this technic can be found in a previous publication.[13] In this manner a series of experiments was performed and permanently recorded by means of motion pictures. The films were subsequently carefully and repeatedly studied by projection with great magnification at a speed one-fifth to one-twelfth that of the original heart rate. Still pictures were made to illustrate the salient features observed in the motion pictures. It should be noted, however, that many observations which were easily made from the slow motion pictures could not be adequately illustrated in the still pictures.

Results:

A. General Observations: After coronary ligation the region of ischemic myocardium soon ceased to contract and it was observed that it appeared to balloon out with each contraction of the surrounding non-ischemic myocardium. We called this phenomenon "ballooning." Distinct ballooning usually appeared 10 to 12 beats after ligation. At first it was confined to a small region near the apex of the left ventricle but gradually it became more extensive in area. Maximum ballooning ultimately involved a considerable portion of the anterior wall of the left ventricle (figures 1 and 2).

When the artery was tied more proximally, i.e., close to its origin, ballooning of the ischemic myocardium was constant. However, when the tie was placed more distally from its origin, ballooning sometimes did not occur at all; if it did occur it was very slight and inconstant.

Slight ballooning, appearing early after coronary ligation, usually about 15 seconds after the artery was tied, could best be distinguished during systole, by noting an increase in the distance between two adjacent vessels on the epicardial surface of the ischemic myocardium. Prior to coronary artery

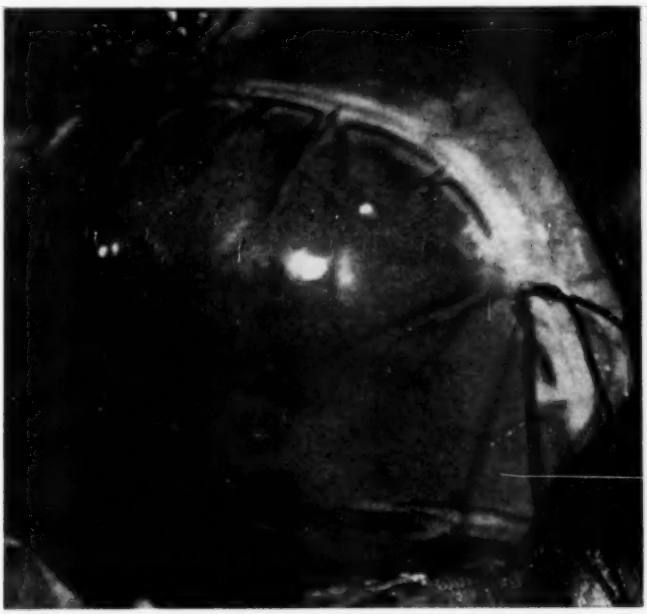

FIG. 1. Photograph of a dog's heart taken in full systole. The anterior descending artery has been ligated. The ischemic myocardium supplied by the ligated artery has ceased to contract and balloons outward in systole.

ligation, the distance between these vessels during systole remained unchanged or became less than it was during diastole. In figure 3, the gradual onset of ballooning after coronary ligation is illustrated. Single frames of motion picture film were projected by means of a still projector. From these projections, in which the heart was enlarged four times, tracings of the heart border and the surface vessels were made at the height of ventricular systole, before the artery was ligated, and 3, 5 and 10 seconds, respectively, after the artery was tied. These figures illustrate the gradual increase in distance be-

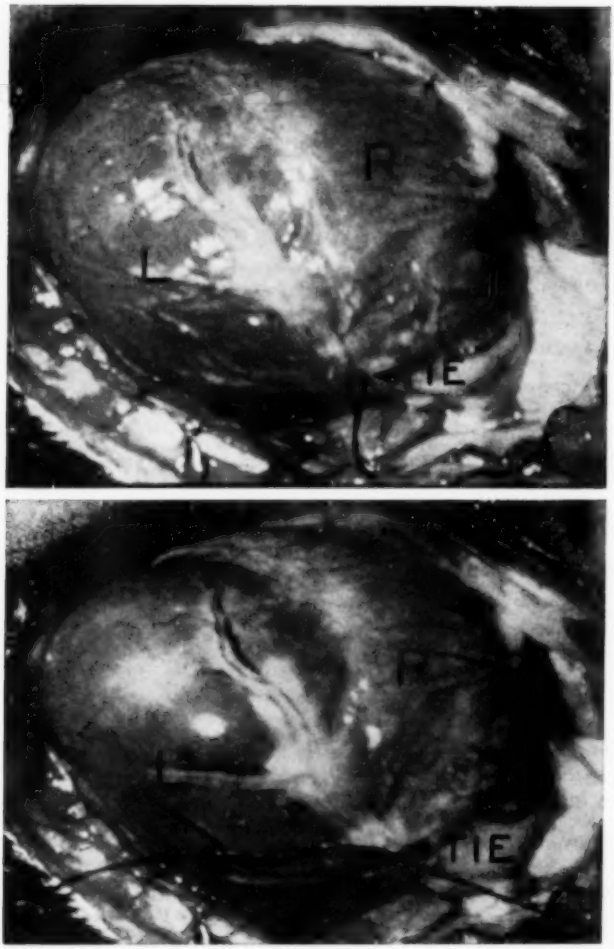

FIG. 2. Photographs of a dog's heart taken in full systole. *Above*, before ligation of the anterior descending artery. *Below*, following ligation, the ischemic myocardium balloons outward in systole.

tween the two vessels on the pericardial surface of the ischemic region during systole, and thus indicate the gradual onset of ballooning soon after coronary ligation. It should be noted that at this time the ballooning is not extensive enough to affect the measurements of the outline of the heart. This may be the reason why Tenant and Wiggers [1] did not note loss of contractility until a minute after ligation of the coronary artery. Their conclusions were based

solely upon changes in the heart outline. Maximum ballooning involved a more extensive area of myocardium, and with its development the outline of the heart during systole was distorted. In addition, the ballooned region assumed a smooth globular appearance in contrast to the wrinkled undulated surface this area exhibited before the coronary artery was tied.

The surface area of myocardium involved in the ballooning even when it was most intense, generally appeared to be smaller than the portion of muscle supplied by the anterior descending branch of the left coronary artery. The reason for this is that anastomotic vessels now are nourishing the periphery of the affected area sufficiently to prevent loss of contractility and subsequent ballooning of these only partially ischemic portions of the involved myocardium.

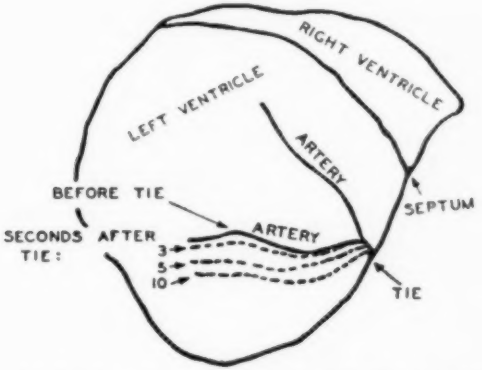

FIG. 3. Onset of ballooning. Tracings made from individual motion picture frames of the branches of the anterior descending coronary artery before, and 3, 5 and 10 seconds after, the ligation of the anterior descending coronary artery. The movement of the lower arterial branch is depicted by the dotted lines and reveals the increasing distance between the two branches caused by the ballooning of the ischemic myocardium.

The ischemic region of the right ventricle always contracted following the arterial tie. This again demonstrates a better collateral circulation to the right ventricle than to the left.[13]

B. Late Systolic Ballooning of the Ischemic Region: At the onset of ballooning, three to 10 seconds after coronary ligation, the ischemic region was generally observed to contract early in systole and balloon late in systole. This early systolic contraction and late systolic ballooning of the ischemic region persisted without progression or intensification throughout some of the experiments. In other experiments, however, the ballooning gradually became more intense until it occupied the whole of systole. Early systolic ballooning with late systolic contraction was never observed. This is demonstrated in figures 5 and 6, in which curves were constructed from measurements of the distance between the two adjacent vessels on the epicardial sur-

face of the ischemic region. Similarly, a curve of the measurements of the same vessels before coronary ligation was constructed for comparison (figure 4).

Sussman, Master, and Dack [4, 5] have made similar observations in patients with coronary occlusion and myocardial infarction by means of cardiac

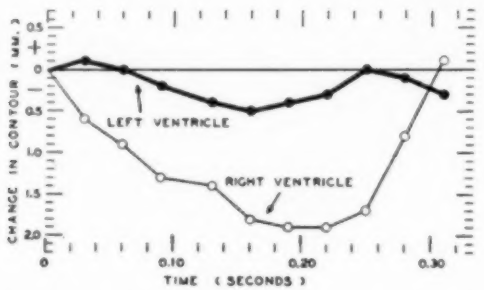

FIG. 4. Normal heart. Graphic representation of changes in contour of left and right ventricle during one complete cardiac cycle. Measurements are made from individual motion picture frames at intervals of 0.03 second. This demonstrates that the left and right ventricles gradually decrease in size to a minimum (full systole) at approximately 0.16 second and 0.19 second respectively, and return to the base line (presystolic state) at about 0.3 second. These measurements are taken from two dimensional pictures and do not indicate all the dimensional changes which occur in the ventricles.

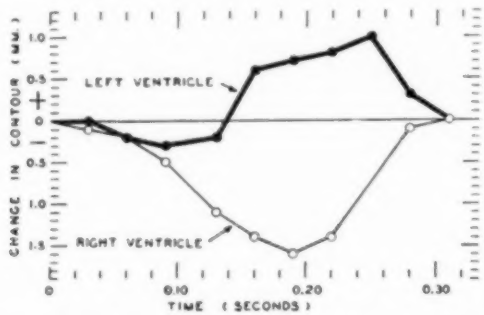

FIG. 5. Late systolic ballooning. Change in contour of same heart as figure 4 during one complete cardiac cycle, 15 seconds after ligation of anterior descending branch of left coronary artery. Contour determined as in figure 5. This demonstrates that the dimensions of the right ventricle are similar to those seen in the normal heart. However, the left ventricle now contracts early in systole and balloons suddenly late in systole. At 0.3 second the ventricle has returned to its presystolic state.

fluoroscopy and roentgenkymograms of the heart. They observed dilatation of a portion of the left ventricle only late in systole in some patients and throughout systole in others.

C. Different Types of Ballooning in the Same Heart: In some experi-

ments, after coronary ligation, it was observed that the central portion of the ischemic region exhibited marked ballooning throughout systole while the surrounding peripheral portion of ischemic myocardium contracted early in systole and ballooned slightly, late in systole. Such variations in non-contractility in the same heart are probably related to the degree of ischemia of the involved myocardium.

The simultaneous appearance of different types of ballooning in the same heart may well explain some of the bizarre roentgenkymograms which are otherwise difficult to interpret.

D. Spontaneous Resumption of Contractility by the Non-Contractile Myocardium: In the course of the preceding experiments it was frequently observed that ballooning disappeared and the non-contractile myocardium

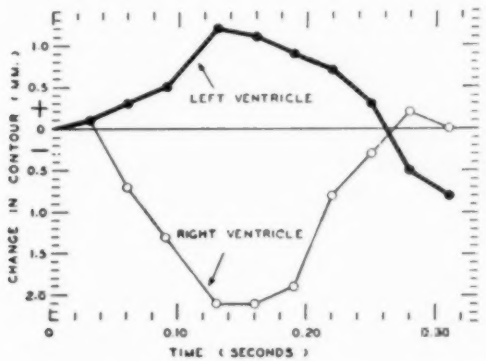

FIG. 6. Ballooning throughout systole. Change in contour of same heart as figure 5 during one complete cardiac cycle, 30 seconds after ligation of anterior descending branch of left coronary artery. Contour determined as in figures 5 and 6. Again the right ventricle contracts normally, but the left ventricle now balloons throughout systole.

spontaneously regained its contractility a few seconds later. In many instances in which well-marked ballooning was established, the contractions of the ischemic non-contractile region spontaneously reappeared, as long as 30 minutes after the ligation. For example, in one experiment, ballooning appeared 12 beats after the artery was ligated and then disappeared after 30 seconds. Two minutes later, however, the ballooning had reappeared, only to disappear again after 15 minutes. Thus, ballooning often waxes and wanes. The cause of this remarkable phenomenon of waxing and waning is not known. It may be due to variations in coronary blood flow produced by varying degrees of coronary spasm or to unknown neurogenic factors. It is of interest to note that we have observed similar waxing and waning of ballooning of the involved myocardium in human beings with coronary artery disease.

When the anterior descending artery is ligated near the origin and the ischemic region is very large, we have never observed spontaneous disappearance of ballooning. This probably is due to the fact that the collateral circulation is not adequate to supply so large an ischemic area.

It is of interest that Lewis [15] has observed reëstablishment of myocardial contractility in some dogs. Gregg et al.[16] noted the resumption of contractions in a region of a non-contractile dog's myocardium seven weeks after occlusion of the arterial supply to that area. However, in this instance, even though observations were made seven weeks later, it must not be concluded that resumption of contractility did not occur earlier.

Part II. Demonstration That the Non-Contractile Region Can Contract

In the preceding experiments we showed that the region of myocardium rendered ischemic by coronary artery ligation quickly lost its contractility.

The question next arises as to whether the ballooned non-contractile myocardium could be made to contract under special conditions. The following experiments were performed in an attempt to answer this question.

Method: In eight dogs, the heart was exposed in the usual manner. A very fine copper wire, enameled except at its two ends, was attached at one end to a Phipps and Bird inductorium. The other end was carefully inserted through the epicardium in the center of the expected ischemic region so that during systole only a few myocardial fibers could exert any pull or pressure on the heart. Motion pictures were taken of the heart at 48 to 64 frames per second during ligation of the anterior descending branch of the left coronary artery, and again subsequent to establishment of marked ballooning during electrical stimulation with make and break currents. A flashlight bulb in the primary electrical circuit was placed in the photographic field, and, by flashing with each contact, indicated the exact time of each electrical stimulus.

Results: Electrical stimuli produced by the above method caused ventricular premature beats. In some cases the ischemic region was observed to contract along with the premature systolic contraction of the rest of the ventricle (figure 7). In other instances, the ischemic region did not contract and ballooned more markedly than during normal contraction of the ventricles. The latter observation is in agreement with that of Tenant and Wiggers [1] who found that extrasystoles did not cause contraction of the ischemic region. We do not know why the ischemic muscle contracts with some premature systoles and balloons with others.

In addition, it was observed that contraction of the ischemic region usually occurred with the first beat of the heart following the compensatory pause after electrically induced ventricular extrasystoles. This is demonstrated graphically in figures 8, 9 and 10 in which tracings of the outline of the same heart in maximum systole and maximum diastole are superimposed

at the following times: (1) before coronary ligation, to show normal contraction; (2) 30 seconds after the arterial tie, to show marked ballooning; and (3) during the first beat following the compensatory pause, to show contraction of the ischemic region similar to that in the normal heart. Since the ischemic region which had spontaneously ceased to contract shortly after coronary occlusion definitely contracted at times in response to electrical

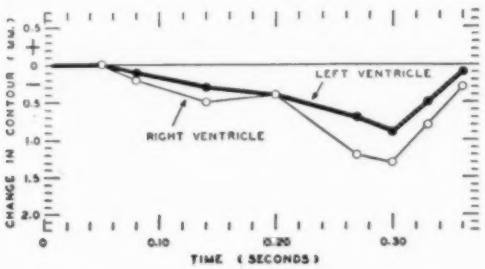

FIG. 7. Contraction of heart after compensatory pause following electrically induced extrasystole. Change in contour of same heart as previous three figures during part of compensatory pause and subsequent systole. Cycle is longer than normal due to initial compensatory pause. It can be seen that the left ventricle which ballooned in figure 6 now contracts similar to its contraction in figure 4 before the tie.

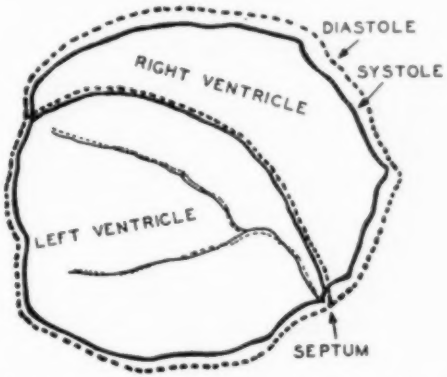

FIG. 8. Normal dog heart. Outline of the heart and anterior descending artery in maximum systole (solid line) and in diastole (interrupted line). The overall dimensions of the heart normally decrease in systole.

stimulation, and also contracted spontaneously during the first beat after the compensatory pause following ventricular extrasystole, it is concluded that this region *in situ* did not lose its ability to contract.

The fact that the ischemic, non-contractile region retains its ability to contract was further demonstrated by the following experiments in 11

dogs. The ballooning, non-contractile portion of myocardium was removed from the heart and placed in a petrie dish filled with saline. Vigorous contractions occurred following electrical stimulation. In some instances the isolated sections of the ischemic myocardium contracted as well as control non-ischemic regions of the same heart following electrical stimulation. These segments could be made to contract up to 45 minutes after they were cut out.

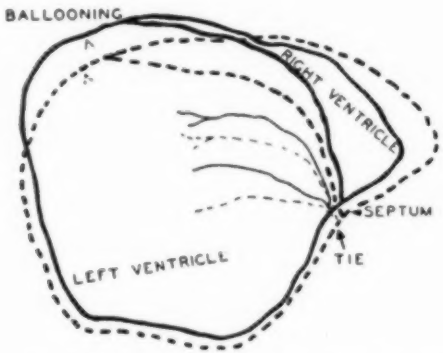

FIG. 9. Same heart as in figure 8 after ligation of anterior descending artery. During systole the ischemic portion of the left ventricle balloons.

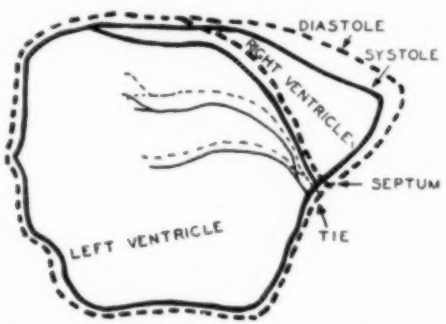

FIG. 10. Same heart as in figure 9, outlined in the contraction after a compensatory pause following electrically induced extrasystole. The ischemic region contracts as well as in the normal heart (figure 8).

This crude experiment together with the electrically induced extrasystole experiment outlined above demonstrates that the failure of the ischemic area to contract with cardiac systole does not necessarily represent a fundamental loss of muscle contractility. In other words although contractility during normal systole may be lost, the ability to contract under other circumstances may be retained.

Part III. Demonstration That the Non-Contractile Region Retains Conductivity

It has been suggested that the loss of contractility of the ischemic myocardium *in situ* is due to loss of the ability of this region to conduct the impulse for contraction. Harris and Matlock [17] found slowed myocardial conduction and diminished myocardial excitability in dogs with severe anoxia produced by the inhalation of gases with markedly reduced oxygen content. Drury [18] observed that increasing amounts of extreme pressure on an atrium of the dog's heart caused first a delay in conduction, leading sometimes to a two to one heart block, and finally complete interruption of conduction. Since this compression of the atrium causes, among other effects, diminution of the blood supply to the auricle, it appeared possible to explain this loss of conductivity on a basis of ischemia. Alteration or interruption of the conduction of the impulse to the ischemic region could therefore result in loss of contraction in this part.

In order to determine whether the non-contractile ischemic myocardium retained or lost its ability to conduct the impulse for contraction, the minimum strength of the electrical stimulus which was required to produce a ventricular extrasystole when applied to the ischemic region, was determined before and at various periods of time after ligation of the anterior descending branch of the left coronary artery in five dogs. By means of the

Table I

Dog No.	Time after Arterial Ligation (min.)	Minimum Stimulus Required for Extrasystoles*
707	− 2	L 3
	0	—
	1	L 3
	3	L 4
	4	L 4
	7	L 4
	19	L 4
712	− 2	L 3
	0	—
	5	L 3
	12	L 3
	17	L 3
714	− 2	L 3
	0	—
	1	L 3
	4	L 3
715	− 6	L 3
	0	—
	1	L 3
	6	L 3
	17	L 3
716	− 5	L 2
	0	—
	4	L 2
	5	L 2

* Single break induction shock in arbitrary units, reading of Phipps and Bird Inductorium. Increased voltage is represented by increased numerical value (L 4 is greater than L 3, etc.).

electrical setup described in Part II, the minimum current necessary to produce a ventricular extrasystole before coronary ligation was compared with the weakest effective electrical stimulus required to produce an extrasystole for a period of time up to 19 minutes after ligation. It was found that the minimum strength of the electrical stimulus which was effective in producing a ventricular extrasystole remained constant at all times tested before and after coronary ligation (table 1).

It seems, therefore, that the function of conductivity in the ischemic region *in situ* is retained apparently unaltered for at least 19 minutes after coronary ligation. Tenant and Wiggers [1] also showed that the conductivity of the ischemic portion was unimpaired even though contractility of the region was lost. Their experiment was not a quantitative one.

TABLE II

Dog No.	Time after Arterial Ligation (min.)	Minimum Stimulus Required for Contraction of Excised Myocardium*	
		Normal	Ischemic
522	20	L 2	L 2
	30	L 2	L 2
	40	L 3	L 3
	50	L 3	L 3
	65	H 10	L 4
616	25	L 2	L 5
	40	H 10	H 10
617	25	L 3	L 2
	35	L 10	L 3
	40	H 5	H 8
618	25	L 1	L 2
	35	L 3	L 2
	40	H 5	L 8
	50	H 10	L 8
619	7	L 3	L 3
	15	H 10	L 1
	25	H 10	H 10

* Single break induction shock in arbitrary units, reading of Phipps and Bird Inductorium. Increased voltage is represented by increased numerical value; e.g., L 3 to L 4, and change of letter, L (low) to H (high).

So far, it has been demonstrated that an *artificial* impulse applied to the ischemic region can be conducted from this region to the rest of the ventricular myocardium. It may be, however, that the *natural* impulse for contraction beginning at the S-A node and traversing the ventricular myocardium is not conducted into the ischemic region. We believe that the natural impulse does reach the ischemic region, because shortly after coronary ligation there is usually a spontaneous early systolic contraction of the ischemic region, or an effort to contract, with late systolic ballooning.

Under conditions of extreme ischemia of cardiac muscle, when the muscle was cut out of the heart, we noted reduced conductivity. This is illustrated in table 2. In five of the experiments in Part II, in which the ischemic region was cut out of the heart, the strength of the electrical stimulus required to produce a contraction increased within 5 to 50 minutes. This was also true for the strength of the electrical stimulus required to produce a contraction in isolated portions of previously normal myocardium. The conditions of these experiments probably parallel more closely the conditions in the experiments described by Harris and Matlock.[17] It should be emphasized that impaired conductivity was found only in experiments in which pieces of myocardium were isolated and therefore entirely devoid of blood supply; in experiments performed *in situ*, probably because the ischemic myocardium received a collateral blood supply, no impairment of conductivity was observed.

Part IV. Effect of Increased Work on Ballooning

Patients with coronary artery disease, during their daily activity, must continually perform functions which increase the work of the heart, either by increasing blood pressure, cardiac output, or both.

In order to determine whether or not such increase of cardiac load has a deleterious effect on the contractility of ischemic myocardium, a coronary artery was partially tied in the distal third of its course to reduce its lumen. We have shown that little or no ballooning occurs in such a preparation if the blood pressure remains normal.[14] To increase the work of the ventricle, a large clamp was placed on the aorta, causing a marked narrowing of its lumen. This, of course, greatly increases the work of the left ventricle by raising the blood pressure to extremely high levels. It was found that if ballooning was not present before this procedure, it occurred during the increased work of the heart. If ballooning was present before the work of the heart was increased, the ballooning was greatly intensified during the acute hypertension. Obviously, loss of contractility has a deleterious effect upon the heart, because a large section of the myocardium loses its pumping function and thereby imposes an added burden upon the remaining contractile portions of the left ventricle. This experiment is a direct demonstration of the deleterious effect of increased work on the damaged heart. If the increased work is extreme, and the coronary arteries are diffusely diseased, it is easy to understand how death or heart failure may ensue. The importance of avoiding anything which increases the work of the heart in patients with coronary insufficiency is apparent.

In a previous communication[14] we have observed that decreasing the blood pressure by hemorrhage caused an increase in the ballooning. This is caused by marked diminution of the collateral circulation through the intercoronary anastomoses resulting from lowering of the pressure gradient. In the present experiment, however, raising of the blood pressure likewise

caused an increase in ballooning, if the heart was subjected to ischemia by interference with the coronary circulation. The increase in ballooning in the present experiment is more difficult to explain. One cause might be increased intraventricular tension which could accentuate ballooning in the presence of some loss of contractility. Another cause might be the degree of coronary insufficiency. Raising the blood pressure in a normal heart may be expected to increase the coronary blood flow which would compensate for the increased work and thereby prevent coronary insufficiency. Likewise, in the presence of a partial coronary ligation, a rise in blood pressure will increase the pressure gradient through the anastomotic vessels and thus facilitate the flow of blood through the partially ligated artery. However, in the present instance, it would seem reasonable to assume that because of the high degree of coronary obstruction the increased pressure is unable completely to compensate for the increased work resulting from the high pressure. Thus, the high degree of coronary insufficiency, together with the increased pressure in the left ventricular cavity, may be the cause for the increase in ballooning in the present experiment.

Part V. Preliminary Clinical Observation of Non-Contractility of Ischemic Myocardium

Some clinical observations on the contractility of heart muscle following acute coronary occlusion have been previously reported. Dack et al.[5] and Sampson [19] and Thomas and Garland [20, 9] studied patients with acute coronary occlusion by means of cardiac fluoroscopy and roentgenkymography, and noted regions of non-contractility on the left ventricular border of the heart. In some cases, after variable periods of time, the non-contractile areas were no longer seen. This was explained to be a result of retraction of the non-contractile heart muscle consequent to scar formation in the area of myocardial infarction.[19] However, this mechanism does not explain the results of our experiments in dogs in which spontaneous resumption of contractility in non-contractile ischemic myocardium often occurred within one minute after coronary ligation.

As an outcome of the preceding animal experiments on myocardial non-contractility following coronary ligation, it was decided to investigate the possible clinical application of these findings in selected patients with coronary artery disease by means of cardiac roentgenkymography. Because these clinical studies represent an extension of the preceding experimental data, the following preliminary observations are reported at this time.

Case 1. A 57 year old white male who had previously been in good health had a severe attack of precordial pain which lasted 36 hours. A roentgenkymogram of the heart taken two days after the onset of pain revealed definite non-contractility and questionable dilatation of a portion of the left ventricular border (figure 11). The electrocardiogram at this time was normal. On the following day, this area of non-contractility was no longer seen, and there was definite pulsation of all the heart borders (figure 12). Subsequent films on the eighth and eighteenth days revealed

questionable diminished contractions in the involved region. A final film taken two months after the first again revealed systolic dilatation of a portion of the left ventricular border more marked than that observed in the original film. In addition it was noted in this film that in the center of the involved region dilatation occurred throughout systole, whereas at the periphery dilatation occurred only in late systole. Electrocardiographic changes first appeared on the sixth day and progressive changes occurred up to the twenty-fifth day, indicating posterior myocardial infarction. After the twenty-fifth day there were no further alterations in the electrocardiogram.

FIG. 11. Roentgenkymograms of patient taken two days after the onset of precordial pain. Note loss of contraction of left ventricle.

There was no correlation between the electrocardiographic changes and the alteration in myocardial contractility. This suggests that the electrocardiographic changes associated with myocardial infarction are not necessarily related to changes in contractility of ischemic myocardium.

The recovery of contractility in this case only one day after the onset of non-contractility presents further evidence that this recovery is not caused by retraction of the myocardium consequent to scar formation. The ob-

servation that contractility in this case was absent on the second day and reappeared on the third day led to a correct diagnosis of coronary occlusion although there were no electrocardiographic changes at this time.

Case 2. The second patient, a 44 year old male, had a typical history of angina pectoris for four months. His cardiac roentgenkymogram revealed normal pulsation of all borders on postero-anterior view. Following exercise consisting of brisk walking sufficient to induce anginal pain, a second roentgenkymogram revealed an area of diminished contractility on the left ventricular border.

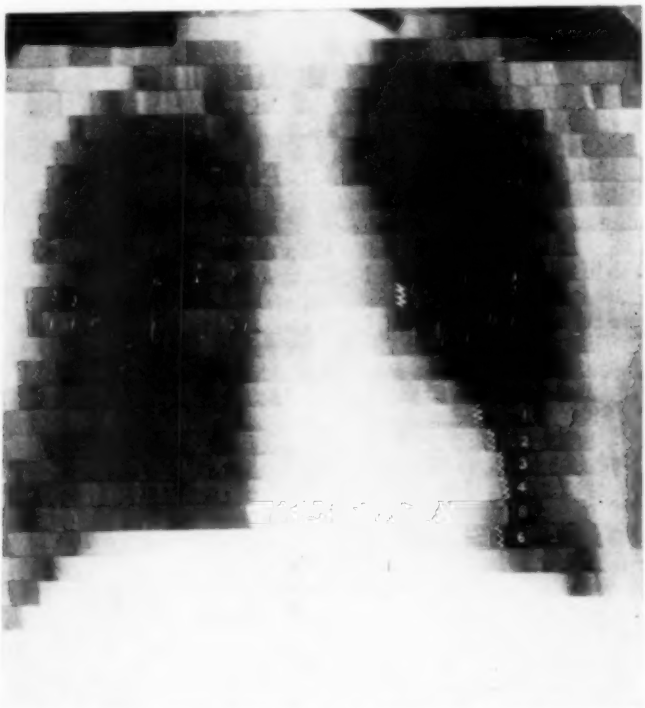

FIG. 12. Roentgenkymograms of same patient as in figure 11, taken the next day. Note normal contractions of the left ventricle. Roentgenkymograms taken on subsequent days again revealed loss of contraction of left ventricle. This demonstrates that in the human being with coronary occlusion, ballooning may be an inconstant phenomenon.

Case 3. A third patient with typical angina pectoris for two months and EKG changes indicative of coronary insufficiency on exercise showed no roentgenkymographic changes with pain after exercise.

It may be concluded that diminished or absent contractions of the myocardium as seen by roentgenkymography may occur in coronary disease and

be of diagnostic importance. The absence of such changes, however, does not rule out coronary disease.

These observations will be extended, especially in cases of angina pectoris. It is believed that if diminution of myocardial contractility occurs during exercise-induced attacks of pain, such changes may be of diagnostic value in selected cases.* These clinical observations confirm the experimental observations that myocardial non-contractility may be temporary and may be induced with increased heart work.

Discussion

Early in the course of our investigation, it was observed that ballooning did not always occur following coronary artery occlusion, and when it did it was often intermittent. This at first was difficult to understand, but after further investigation it was found that if the tie was made distally along the course of the artery so that only a small region of myocardium was ischemic, the myocardium often contracted normally and ballooning did not occur. It was reasoned that if the coronary arteries are end-arteries, ballooning of the ischemic myocardium would have resulted if its nutrient arteries were completely occluded. However, the ischemic region continued to contract. This is interpreted as complete proof that the coronary arteries are not end-arteries, physiologically. In the few instances in which ballooning did occur following a distal ligation it is possible that the pressure gradient of the interarterial anastomosis was reduced by the shock-like state produced by the surgical procedure. It was demonstrated in previous studies on shock that when the blood pressure was reduced, ballooning which was previously not present, or was slight, was intensified.[14] When a coronary artery was ligated near its origin, so that a large region of myocardium became ischemic, ballooning was a persistent phenomenon. This is explained by our previous studies on coronary anastomoses.[14] The region of ballooning was always found to be smaller than the region supplied by the coronary artery. This was because the blood entering by way of the collateral circulation enters the periphery so that the peripheral myocardium is more adequately nourished and therefore continues to contract. In ligations of intermediate sized arteries, ballooning often was an intermittent phenomenon, coming and going every few seconds. Undoubtedly sufficient blood intermittently entered the ischemic myocardium normally supplied by the occluded vessel to allow it to contract. This intermittency is also proof that the coronary arteries are not end-arteries.

These experiments were conducted in dogs in which coronary sclerosis was not previously present. It is well established that the intercoronary anastomoses are larger in humans in whom coronary sclerosis is present.

* We have recently observed several patients with chest pain whom we examined fluoroscopically before and after exercise. It was found in some instances that non-contractility or systolic ballooning occurred after exercise which was not present before.

Therefore, the physiological importance of the intercoronary anastomoses in the human is greater than that described in this study and possibly would modify and diminish the occurrence of non-contractility to a greater extent.

In this investigation it was observed that the region of the heart supplied by an occluded artery ceased to contract, usually within about five seconds after the occlusion. It is generally claimed that this non-contractility is caused by the ischemia of the myocardium. However, it was demonstrated that such non-contractile ischemic myocardium is still able to contract when isolated and stimulated electrically, and *in situ* when stimulated mechanically and electrically. In addition, it was observed that contractility may spontaneously recur intermittently in the non-contractile ischemic region. What, then, is the explanation for this phenomenon of non-contractility?

Loss of conductivity could be offered as a possible cause for the non-contractility of the ischemic myocardium. The evidence is against this assumption. It was demonstrated that the spontaneous impulse does reach the ischemic region following the occlusion because (1) the ischemic region exhibits early systolic contraction or effort to contract and late systolic ballooning; and (2) contractility recurs spontaneously. It was also shown under the conditions of these experiments that (1) the ischemic region conducts an impulse, and (2) there appears to be no diminution in conductivity following the onset of ischemia.

Another theory which may be offered to explain the phenomenon of non-contractility is that in ischemic myocardium contractility is weakened. It has enough strength to start the contraction during early systole when the intraventricular pressure is relatively low; however, late in systole, with the intraventricular pressure high, the ischemic muscle becomes fatigued and the contraction cannot be maintained. This work theory would likewise explain the contractility of ischemic myocardium when it is cut out and stimulated. Here it has no opposing force and its work is much less than in the heart.

On the other hand, the ischemic region *in situ* usually contracted most efficiently in the systole after the compensatory pause, at which time the ventricle contained more than the usual volume of blood and therefore required a more forcible contraction to oppose the increased intraventricular pressure. Perhaps this may be explained on the basis that the pause allowed greater recovery of the ischemic myocardium. However, this explanation cannot be accepted without reservation, since the ischemic region contracted equally well during interpolated extrasystoles when the preceding period of relaxation was shorter than normal. The work theory also offers no explanation why the ischemic region spontaneously regained its contractility from time to time with no discernible change of conditions.

Under the conditions of these experiments, therefore, we are unable to ascertain the mechanism of non-contractility. From the available evidence,

the "work" theory seems to be the most logical; however, at present we cannot reconcile all the evidence with such a theory.

Regardless of its mechanism, this phenomenon of cessation of contraction of the ischemic myocardium if limited in extent, may be considered protective in nature. Since the metabolic needs of contracting muscle are much greater than the needs of resting muscle, non-contractility of an ischemic region of myocardium would appear to be advantageous in preserving the damaged muscle.* However, when the area of non-contractility is larger, the resulting hemodynamic changes may become a serious complicating factor. For example, when shock occurs following a coronary occlusion with its attendant drop in blood pressure, the blood supply to the myocardium not directly involved by the occlusion may be sufficiently embarrassed so that non-contractility becomes very extensive. Such a course of events might constitute a cause of sudden death following coronary occlusion clinically. This has been discussed more fully in previous studies.[14]

Patients with acute coronary occlusion frequently experience spontaneous disappearance and resumption of pain. Since ischemic myocardium does less work when it becomes non-contractile, possibly the spontaneous intermittency of contractility is related to the spontaneous intermittency of pain clinically.

The phenomenon of non-contractility with intermittent resumption of contractility noted in the experimentally induced ischemic myocardium in dogs was also observed in one patient with myocardial infarction of the posterior wall, and in one patient with angina pectoris after typical pain was induced by exercise. In the first case, the electrocardiographic changes did not appear to be correlated with the changes in contractility. There was evidence of loss of contractility in the first roentgenkymogram taken 36 hours after the onset of pain. The next roentgenkymogram showed resumption of contractility. Throughout this period the electrocardiogram remained normal. Because of our experimental observation in dogs that ballooning may appear and disappear following coronary artery occlusion, we made a definite diagnosis of coronary occlusion on this patient in the presence of a normal electrocardiogram. This diagnosis was confirmed by the development of typical electrocardiographic changes eight days later. In the patient with angina pectoris who developed loss of contractility after exercise the situation may be comparable to that of our dog experiments in which a coronary artery was ligated in the distal third of its course. In such a case no ballooning occurred until the work of the heart was greatly increased. It is possible that temporary loss of contractility may be a frequent occurrence in patients with coronary artery disease following exercise or increased work. If this be true, detection of such loss of contractility

* We actually have no proof that the non-contractile muscle is "resting." It may be making a feeble effort to contract but this contraction is so weak that it is easily overcome by the systolic intraventricular pressure.

could prove a valuable diagnostic aid in patients with intermittent chest pain of unknown etiology. This point merits thorough investigation.

Atypical systolic murmurs are often found in patients following coronary artery thrombosis, for varying periods of time. A possible explanation for the occurrence of these murmurs is that in systole the blood eddies in the ballooning myocardium creating the abnormal sounds.

In view of our observations in the dog on the effect of the size of the artery occluded and the presence of ballooning, the following clinical phenomena are suggested: (1) If ballooning is not present in a patient following chest pain, it does not prove that coronary artery occlusion has not occurred. It may have been a small distal artery that has been occluded, with little or no reduction in blood pressure caused by shock. In such instances, in our experimental studies, we have demonstrated that ballooning may not occur. (2) If the ballooning is intermittent, that is appearing one day and disappearing the next, then probably a medium size vessel is occluded. This was observed in patient 1 of our series (figures 11 and 12). (3) If ballooning occurs immediately after the onset of precordial pain and persists from that time on, it suggests that a larger artery has been occluded. However, if shock is present the ballooning is intensified.

Conclusions

1. Myocardial contractility was studied by means of slow motion color pictures in dogs after coronary occlusion.

2. Following coronary artery ligation, the ischemic myocardium may become non-contractile in as little as five seconds after the ligation.

3. In some experiments, under certain circumstances following coronary occlusion, the ischemic region continues to contract. This conclusively proves that the coronary arteries physiologically are *not* end-arteries.

4. The ballooning of the ischemic region may spontaneously appear and disappear. This also proves that the coronary arteries are not end-arteries.

5. The ballooning may occur only later in systole, the ischemic region contracting early in the first phase of systole and bulging out in the last phase of systole. Full systolic ballooning and late systolic ballooning may occur simultaneously in different regions of the same heart.

6. The non-contractile portion may be made to contract during and following electrically induced premature systoles.

7. Electrical conductivity to and from the ischemic region does not appear to be impaired.

8. An increase of the work of the heart as a result of a rise of blood pressure caused by constriction of the aorta may cause increased ballooning of ischemic myocardium. The clinical importance of this observation in so-called coronary insufficiency or failure is obvious.

9. Possible clinical application of this study on non-contractility of the myocardium, which may be of diagnostic value, has been made in two patients with coronary artery disease.

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STUDIES ON THE CORONARY CIRCULATION. VII. THE REMARKABLE RESERVE POWER OF THE HEART *

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Little is known about the reserve contractile power of the heart. This is in marked contrast to the extensive knowledge available in regard to the reserve power of other vital organs. Thus, it is known that animals can continue to live with 25 per cent of one kidney,[1] 40 per cent of one lung,[2] 20 per cent of the liver,[3] 16 per cent of the adrenal cortex,[4] and 6 per cent of the small intestine.[5] In the case of these organs, the method of investigation is technically easy. In serial experiments upon the same or successive animals, increasing portions of the organ being investigated are removed, until the absolute minimum quantity necessary to sustain life has been determined. Obviously, this procedure cannot be followed in the case of the heart.

It occurred to us, however, that similar increasing reductions in functional capacity of the heart might be achieved by successive coronary ligations, repeated at intervals of several minutes each. In previous experiments,[6] it was observed that such ligations result in myocardial non-contractility within the regions supplied by the ligated arteries, and that these regions of non-contractility can be accurately studied by the method of slow-motion pictures.

Method: Seven dogs were anesthetized with nembutal and completely atropinized. The mean femoral blood pressure was taken by means of a cannula in the artery connected with a mercury manometer. The chest was opened and the parietal pericardium was incised and sewed to the margins of the incision, thus creating a hammock for the heart. Slow-motion colored pictures of the heart were taken in a manner previously described.[6, 7, 8] All major coronary arteries of the left ventricle were dissected free, and loose ligatures were placed around each artery. The number of ligatures for each heart varied from four to eight. Arterial closures were effected in the following order: (1) The anterior descending branch was always ligated, sometimes first, at other times, last. (2) The posterior descending artery, which runs along the septum between the ventricles, was ligated several minutes later. (3) After this, all the major arteries running along the left auricular ventricular groove, both anterior and posterior, were progressively ligated.

* Read before: The III Interamerican Cardiological Congress, Chicago, June 17, 1948; The American Heart Association, Chicago, June 19, 1948.

Motion pictures of these experiments were shown before: The III Interamerican Cardiological Congress, Chicago, June 17, 1948; The American Heart Association, Chicago, June 19, 1948; The American College of Physicians, San Francisco, April 23, 1948.

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This generally consisted of three arteries posteriorly, one laterally, and one anteriorly about an inch to the left of the anterior descending branch. In one experiment, a large artery to the right of the anterior descending artery supplying the anterior aspect of the right ventricle was also ligated.

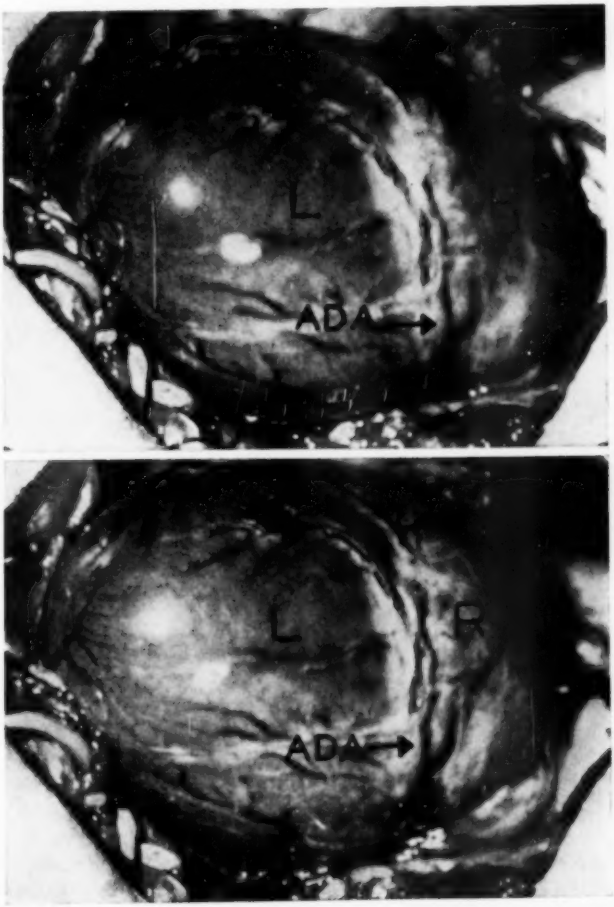

FIG. 1. All the major branches (seven) of the coronary arteries supplying the left ventricle have been ligated. Photographs taken 90 minutes after ligations. Blood pressure 120 mm. Hg. Note that the left ventricle balloons throughout systole and diastole. Approximately 15 per cent of the myocardium of the left ventricle (in the lower left corner) continues to contract and the rest balloons outward. *Above*, taken in full diastole; *below*, taken in full systole. L—left ventricle; R—right ventricle; ADA—anterior descending artery. This experiment can be demonstrated much more clearly in the motion picture.

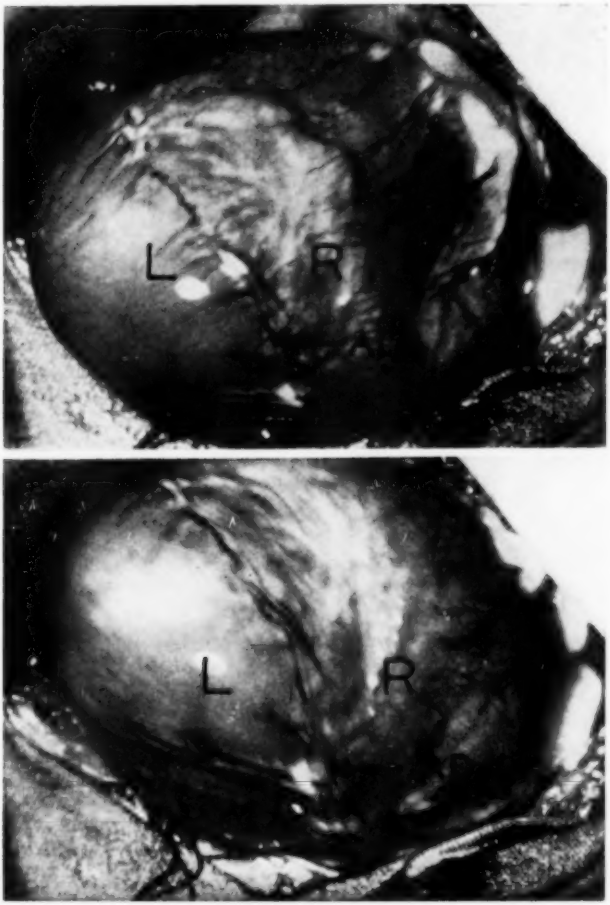

FIG. 2. All the major branches of the coronary arteries of the left ventricle have been ligated. The respiratory pump has been cut off and a rise in blood pressure to 200 mm. Hg occurred. *Above*, taken in full diastole; *below*, taken in full systole.

An interval of approximately 10 minutes was allowed after each ligation. The experiment was carried out successfully on six normal dogs. In the seventh dog, which appeared ill and emaciated, ventricular fibrillation ensued after one simple ligation.

Results: We were surprised to find that the heart continued to beat as long as 90 minutes after all major vessels of the left ventricle had been ligated. By careful examination of successive motion pictures, it was found that larger and larger portions of the left ventricle stopped contracting and

ballooned out in systole. (In some experiments motion pictures were taken in such a manner that the posterior surface of the left ventricle could also be seen.) In some cases the heart continued to beat although only a small portion (approximately 15 per cent) of the left ventricle appeared to contract in systole. Yet, in none of these instances, in spite of the ligation of as many as eight arterial branches, was there a fall in blood pressure below the pre-ligation level; nor was there evidence of failure of the left ventricle, such as pulmonary edema, or dilatation of the right ventricle. Thus, this small segment of the left ventricle was able to perform in an apparently mechanically efficient manner the entire function of the left ventricle (figure 1).

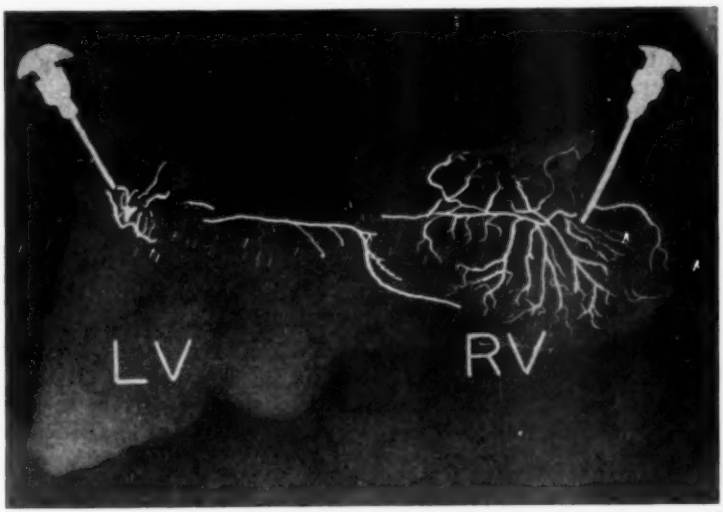

FIG. 3. Roentgen-ray of dog's heart with right and left coronary arteries injected with radiopaque material after ligation of all major coronary arteries of the left ventricle. Note the great diminution in number of patent arteries to the left ventricle. RV—right ventricle, LV—left ventricle.

In one experiment, after the mass ligation was completed, respiration suddenly ceased and asphyxia supervened. The usual asphyxial rise in blood pressure occurred; the mean blood pressure rose to over 200 mm. Hg. Thus, the remaining small segment of contracting left ventricle was able not only to maintain the circulation with normal blood pressure, but in an emergency, when the peripheral resistance was increased, successfully met the increased demand and elevated the blood pressure to almost double its normal value (figure 2).

In two experiments, the extent of the diminution in myocardial circulation after these mass ligations was demonstrated by intravenous injection of fluorescein in the manner previously described (by near ultraviolet light

technic).[7] After the completion of one experiment, the coronary arteries were injected with radiopaque material. Great reduction in the number of patent coronary arteries in the left ventricle was demonstrated by roentgen-ray (see figure 3). It was thus shown that little blood entered the myocardium of the left ventricle. Also, it would appear from the fluorescein experiment that the Thebesian circulation supplied little blood under these circumstances.

Discussion

In this series of experiments, by means of multiple coronary artery ligation, it was found that as little as 15 per cent of the myocardium of the left ventricle seemed to be sufficient to maintain a functionally adequate systemic circulation. The dog's heart is, therefore, analogous to other vital organs, such as the lung, liver, kidney, and adrenals, which can be reduced by more than one-half their total mass without causing death of the organism. That the same thing may be true in human beings is attested by those who have extensive experience with roentgenkymograms. In such observations the participation of only a small segment of myocardium in a systolic contraction is not an uncommon finding.[9] Although roentgenkymography is not nearly so satisfactory a method of investigation as the vivid motion pictures used in this study, nevertheless it affords acceptable evidence that the human heart, like that of the dog, has remarkable reserve power.

There are some clinical applications of the observations described in this study. For example, Leary and Wearn [10] noted that patients survived presumably slowly effected occlusions of both major coronary arteries. These authors assumed that under such circumstances the Thebesian vessels supplied nourishment to the myocardium. Although this possibility cannot be denied, yet it is also conceivable, in view of this study, that in a patient suffering occlusion of both major coronary arteries a small segment of the left ventricle, nourished by collateral blood supply, may be sufficient to sustain normal systemic circulation.

To some extent, our observations may also add to the understanding of cardiac hypertrophy seen in arteriosclerotic heart disease. In widespread damage of the myocardium, when the patient survives, there must remain at least a small portion of muscle which retains its contractility. If the period of survival is long enough, this remaining contracting muscle necessarily undergoes hypertrophy and compensates for the large, non-functioning portion of the heart. Meanwhile, the damaged myocardium becomes increasingly fibrotic, continues to be stretched, and the ventricle becomes greatly enlarged. Dilatation and hypertrophy thus account for the great enlargement often seen in these arteriosclerotic hearts.

These studies may also afford an explanation why life is sometimes maintained in spite of extreme destruction of myocardium in various types of nonspecific or rheumatic diffuse myocarditis. In these instances, viable contractile elements scattered throughout the heart, even though relatively few in

number, may yet be sufficient to carry on a life-sustaining circulation. In the light of the experimental study described above, one muscle fiber in eight able to contract, may be sufficient to maintain life.

Summary and Conclusions

1. In seven dogs all the major coronary arteries of the left ventricle were ligated. As many as eight coronary arterial branches were ligated in one animal.

2. By means of slow-motion colored pictures of these experiments, it was possible to evaluate the amount of myocardium that lost its power to contract. It was found that in dogs as little as 15 per cent of the ventricle apparently is sufficient to maintain adequate systemic circulation.

3. The greatly diminished blood supply to the myocardium, under the conditions of the experiments described above, was demonstrated by intravenous injection of fluorescein and motion pictures taken in ultraviolet light. It would appear that the Thebesian circulation supplied little or no blood under these circumstances.

4. In one experiment, the remaining contractile element was able to maintain an asphyxial rise of blood pressure from 100 to 200 mm. Hg.

5. These observations may offer a possible reason for the development of cardiac dilatation and hypertrophy in diffuse coronary artery disease even in the absence of hypertension. They may also suggest a possible explanation for survival in the presence of occlusion of both major coronary arteries, and for the persistence of life in spite of widespread disease of the myocardium.

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UNIPOLAR EXTREMITY LEADS IN RECORDS WITH LARGE Q_3 *

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Large Q waves in Lead III are an important sign of myocardial infarction and frequently are a permanent remainder of the event after all other abnormalities have disappeared from the electrocardiogram. They may also be the result of chronic degeneration of the myocardium. Since the importance of these waves was pointed out in 1930 [1] and it was recognized that they might be found occasionally in normal hearts, there have been repeated attempts to find criteria to decide whether a large Q_3 in a given record has a normal or abnormal significance. With the advent of the chest leads, data were obtained which, sometimes, helped to decide. If there was a characteristic abnormality of the T wave of the chest leads, a large Q_3 might be considered as being of abnormal significance. In 1933, Wilson introduced the unipolar extremity leads,[2] and it has been suggested by several authors that the VF lead would be of value in deciding the significance of a large Q_3.[3, 4, 5, 6]

Different authors have specified different criteria by which a normal or abnormal state of the myocardium could be diagnosed from the appearance of the QRS and T waves of the unipolar leads from the leg (aVF or VF). Goldberger states that, "In the left leg lead, if the Q deflection has an amplitude of 40 per cent or more of the entire QRS complex, and it has a duration of 0.04 second or more and is associated with a downward T deflection, such a pattern is usually due to posterior infarction. However, similar records, especially if the QRS complex consists of a QS deflection or of a small W-shaped complex, are occasionally met with in cases without infarction." [3] Nyboer states, "Posterior myocardial infarction may be present if, in VF, Q equals 25 per cent or more of R, RS–T is elevated, T is flat or inverted or associated with depressions of RS–T in leads VF and VL." [4] Lyle states, "It is reasonable to conclude that if Q (in VF) is proportionately large or greater than 25 per cent of R in L. L. (VF), we are dealing with a posterior type of infarction. This is particularly true if Q is 0.04 or more seconds and the QRS complex is followed by an inverted T wave, in L. L. (VF)." [5] Myers and Oren found that, "when QLL had 25 per cent or more of the amplitude of RLL, a diagnosis of posterior infarction could be suspected from this alone." [6]

In order to ascertain how much help can be obtained from the unipolar extremity leads in making this decision, we have attempted analysis of 168 electrocardiograms with a Q_3 of sufficient size to be called abnormal accord-

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ing to the Pardee criteria.[1] The conventional limb leads, CF_2, CF_3, CF_5, and aVR, aVL, and aVF [2] were obtained. Of these 168 electrocardiograms 134 had a Q wave in aVF, the size varying from 0.5 mm. to 8.75 mm. (table 1). Fifty-nine of the 168 electrocardiograms were obtained from 34 patients with a diagnosis of posterior myocardial infarction. The size and duration

TABLE I

Size of QaVf in 168 Records

mm.	No.
0 to less than 0.5	34
0.5	10
1.0	22
1.5	15
2.0	17
2.5	14
3.0	14
3.5	3
4.0	8
4.5 to 8.75	31

of QaVF were measured (table 3); its percentage of QRSaVF was determined and these findings were correlated with the form of TaVF (table 2).

Examining these electrocardiograms for Goldberger's three criteria of posterior infarction in the unipolar extremity leads,[3] it is found (table 2) that 45 of the 59 electrocardiograms had a QaVF of 40 per cent or more of the QRSaVF; 35 had a QaVF of 0.04 second or more. In 43 TaVF was in-

TABLE II

Correlation of QaVf Percentage and Time with Form of TaVf

			With TaVf Wave				
			Inverted	Diphasic	Flat	Upright	Total
QaVf 40% or more of QRSaVf (45)	with duration of Q	0.04 second or more	18	1	1	10	30
		less than 0.04 second	9	0	0	0	9
		could not be measured	5	0	0	1	6
		Total	32	1	1	11	45
QaVf less than 40% QRSaVf (11)	with duration of Q	0.04 second or more	2	2	0	1	5
		less than 0.04 second	3	0	0	2	5
		could not be measured	1	0	0	0	1
		Total	6	2	0	3	11
No QaVf	(3)		1	1	0	1	3
Total	59		39	4	1	15	59

verted or diphasic. A Q wave of 40 per cent or more of the QRS and accompanied by an abnormal T occurred 34 times. A combination of all three criteria occurred only 19 times and was absent in 40. If, from this last group, we subtract the cases with QS and W complexes in Lead aVF as recommended by Goldberger, we would have remaining only 13 electrocardiograms which have all the criteria suggested by this author, thus failing

TABLE III

Size and Duration of QaVf in 59 Records from Cases with Posterior Infarction

mm.	0	0.5	1.0	1.25	1.5	2.0	2.25	2.5	2.75	3.0	3.5	4.0	4.5	5.0	5.5	6.0	6.5	7.0	7.5	8.0	8.75
DURATION	0 0 0	0.03	0	0.03	0.01 0.02 0.04 ?	0.04 0.03 0.03 0.05 0.05 0.05* 0.035 0.04	0.05 0.04 ? 0.05	0.04 0.025 0.04 0.03 0.08	0.035 0.04	0.04 ? 0.05 0.035 0.06 0.03 0.04	0.04 0.06* 0.04	0.06 0.05 ?* 0.04	? 0.03 0.07* 0.035	0.05 0.05 0.05	?	?*	0.07* 0.04	0.07 0.07* ?*	0.08*	0.075*	0.07
total	3	1	0	1	4	8	4	5	2	7	3	4	4	3	1	1	2	3	1	1	1

Notes: *qs present; ? could not be measured.

to diagnose the abnormality by these criteria in 46 records. Using the Criteria of Lyle,[5] Nyboer,[4] and Myers and Oren [6] we would suspect infarction from the unipolar leads in 55 records and would not do so in the remaining four.

On studying the conventional limb leads alone in these 59 electrocardiograms, we find that the diagnosis of posterior myocardial infarction could have been made in 58 of them and the single unrecognized one was the last record of a series in which the two previous records were diagnostic. It is evident that the unipolar leads were not helpful in establishing the diagnosis of posterior infarction no matter whether Goldberger's criteria or the other less rigorous criteria were used. Too many records failed to show the supposedly diagnostic criteria.

In the whole group of 168 records there were 29 electrocardiograms whose only abnormality in the limb and chest leads was a Q_3 of a size large enough to be considered abnormal. This type of electrocardiogram is not uncommon and it is with such records that we greatly need aid in deciding whether or not the Q_3 is due to pathological changes. Of these 29 records, there were 12 from patients with a clinical diagnosis of coronary arteriosclerosis having the anginal syndrome or having had cardiac infarction. Seventeen were from patients considered to be without heart disease. The

TABLE IV

Twelve Cardiac Cases with Large Q_3 as Only Abnormality

Number	1	2*	3	4	5	6	7	8	9	10	11	12*	Total
QaVf 40% or more QRSaVf		+					+					+	3
QaVf 0.04 second or more		+					+					+	3
Form of TaVf (inverted, diphasic or isoelectric		+	+	+						+	+		5
Chiefly due to QaVf		+										+	2
Chiefly due to RaVf	+		+	+	+	+	+	+	+	+	+		10

Note: *QSaVF present.

TABLE V

Seventeen Non-Cardiac Cases with a Large Q_3 as the Only Abnormality

Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14*	15	16	17	Total
QaVf 40% or more QRSaVf														+				1
QaVf 0.04 second or more																		0
Form of TaVf (inverted, diphasic or isoelectric									+			+	+					3
Chiefly due to QaVf								+										1
Chiefly due to RaVf	+	+	+	+	+	+	+		+	+	+	+	+	+	+	+	+	16

Note: *QSaVF present.

unipolar leads were studied in these groups to see if they could help in deciding whether the Q_3 was due to pathological changes in the heart or should be considered physiological (tables 4 and 5).

In the 12 records from patients with clinical heart disease (table 4):

A. Three had a QaVF of 40 per cent or more of QRSaVF (cases 2, 7, 12)
B. Three had a QaVF of 0.04 second or more (cases 2, 7, 12)
C. Five had a TaVF which was inverted, diphasic or isoelectric (cases 2, 3, 4, 10, 11)
D. Three had A plus B (cases 2, 7, 12)
E. One had A plus C (case 2)
F. One had A plus B plus C (case 2)

In the 17 records from the cases without heart disease (table 5):

A. One had a QaVF of 40 per cent or more of QRSaVF (case 14)
B. None had a QaVF of 0.04 second or more
C. Three had a TaVF which was inverted, diphasic or isoelectric (cases 9, 12, 13)
D. None had any combination of two or three of the above

In the 12 records from cardiac cases, criterion A was present three times and absent nine times. Criterion B was present three times in this group, actually in the same three records that showed criterion A. It was absent in nine records. Criterion C was found five times in the cardiac cases and was absent in seven records. The combination of A and B alone occurred three times and of A, B and C once. A and C, and B and C did not occur together except when all three criteria were present. In nine records, no combination of two or three criteria appeared. In the records from the non-cardiac cases (table 5), criterion A was found once. This record had a QS deflection in lead aVF, which Goldberger claims should exclude it from the supposedly significant category of Q greater than 40 per cent of QRSaVF. Accordingly its importance in determining the normal or abnormal significance of Q_3 is nullified. Criterion C was found three times and the Q wave was never 0.04 second or more in duration. A combination of two or more

criteria did not occur. It is important to note that in only three of the 12 records from the cardiac cases did the unipolar extremity leads suggest myocardial abnormality. In one of the 17 records from non-cardiac cases, the large size of QaVF may have suggested abnormality. It is evident that but little help and some confusion in diagnosis may arise if these criteria from the unipolar leads are to be used to substantiate the diagnosis.

It has been suggested by Lyle [5] that the unipolar extremity leads may help in another way in determining whether a large Q_3 is or is not a sign of myocardial damage. It will be remembered that, owing to the wiring of the patient to the electrocardiograph, Lead I = VL–VR, Lead II = VF–VR, Lead III = VF–VL. From the above equations, it can be seen that VF enters positively into the equation for Lead III, that is without change of sign so that QaVF tends to produce a downward deflection in Lead III. VL enters negatively into Lead III that is with change of sign, so that RaVL may produce a downward deflection—a Q wave—in Lead III. Thus, Q_3 may result either from an early downward deflection in VF (QVF) or from an early upward deflection in VL (RVL) or from a combination of these. Lyle claimed that herein lies the diagnostic difference between the deep Q_3 that is due to myocardial damage and the deep Q_3 associated with a normal heart, the first being due to QVF and the latter to RVL.

It is important in this connection that three of the electrocardiograms of our patients with posterior infarction, table 2, failed to show any QaVF whatsoever. In all of these, Q_3 was due entirely to a large RVL (2/3 RaVL).[7] In 38 others Q_3 was for the most part (over 50 per cent) due to the potential of RVL. In three records QVF (2/3 QaVF) was large enough to account for 60 per cent or more of the value of Q_3 while in 18, QVF could account for 50 per cent or more of the value of Q_3. In each case the remaining amplitude of Q_3 was accounted for by RVL. In all cases, there was evidence of posterior infarction in the conventional limb and precordial leads, so that the findings in the unipolar leads failed to confirm Lyle's suggestion as to their diagnostic importance and in 70 per cent of the records were contrary to the clinical diagnosis.

Furthermore, if the group of electrocardiograms with large Q_3 as the only abnormality is considered, we find (table 4) that in only two of the 12 cases with a diagnosis of cardiac disease could Q_3 be explained chiefly (over 50 per cent) by QVF while in 10 it was due chiefly to RVL. In only two of these cases did Lyle's criteria indicate the presence of myocardial damage. In the 17 non-cardiac cases with a large Q_3 as the only abnormality (table 5) this was due to RVL in 16 cases and to a large QVF in one. Lyle's criteria here are contrary to the diagnosis in 11 of the 29 cases failing to indicate disease in 10 of the cardiacs and indicating disease in one of the non-cardiac cases.

Since the unipolar extremity leads are unmodified single potentials, it seemed possible that a measurement of the size of QaVF instead of its relation to another value might be a more reliable guide to its normal or abnormal

significance. This was not found to be the case, however, in our series. As is seen in table 3 the size of QaVF varied from 0 to 8.75 mm. and no matter what value was selected as the upper limit of normal we would still find a considerable number of cases below this limit. If we select 2.5 mm., we would find the value normal in 21 cases with posterior infarction; if we set it at 3.0 mm., we would find it normal in 28; at 3.5 mm., we would find it normal in 35; at 4.0 mm., we would find it normal in 38. The criterion that myocardial disease is indicated by a QaVF 40 per cent or more of QRS aVF agrees with the clinical diagnosis as to normal or abnormal heart in 88 per cent of the complete series of 168 records. The criterion of QaVF 25 per cent or more of RaVF agrees in 93 per cent. Therefore, the percentage method appears to be more useful than actual measurements.

Summary and Conclusions

Goldberger's criterion that QaVF should have a value of 40 per cent or more of QRSaVF was only present in about 75 per cent of the records from cases with infarction. In almost 60 per cent QaVF had a duration of 0.4 second or more while about 70 per cent had an inverted or diphasic TaVF. A value for QaVF of 25 per cent or more of RaVF was present in 94 per cent of these records. On the other hand 98 per cent of the records afforded a positive diagnosis of infarction from the conventional limb Leads I, II and III. The unipolar leads were less useful and in no case afforded the only abnormal diagnostic feature.

The failure of QaVF to have the features considered significant of disease in so many of the records from patients with infarction makes it probable that it would be equally unreliable in determining the presence or absence of disease in those doubtful cases which have Q_3 as the only abnormality of the electrocardiogram. This seems in fact to be the case since only 25 per cent of the group with a diagnosis of coronary arteriosclerosis showed the expected signs. It is difficult to appraise the significance of the one case supposedly without cardiac disease and yet showing QaVF more than 40 per cent of QRSaVF because this record had a small QS deflection in aVF and therefore might not have an abnormal significance.

It is apparent that criteria derived from the unipolar limb leads are not dependable in the diagnosis of posterior infarction. The conventional limb leads more often give a positive sign.

Unipolar limb leads are even more undependable in helping to recognize which records with large Q_3 as the sole abnormality are derived from patients with coronary arteriosclerosis.

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IMMUNOLOGIC TYPES OF BLASTOMYCOSIS: A REPORT ON 40 CASES *

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Although sporadic cases of blastomycosis are found throughout the United States and Canada, the disease has been reported most frequently from the Mississippi Valley and the southeastern states. Durham, N. C. is near the center of the southeastern endemic area and over 50 cases have been studied in the Duke clinic in the past 18 years.

Approximately 45 per cent of the infections were confined to the skin, 45 per cent invaded the internal organs and, in 10 per cent, both the skin and internal organs were involved.

The prognosis seems to depend, at least in part, upon the immunologic status of the patient. Some patients develop humoral antibodies, which can be detected by the complement fixation test, and others acquire a hypersensitivity to the antigen of the organism as shown by the presence of a positive skin test either to a vaccine or to blastomycin.[1] The following combinations of immunologic reactions are theoretically possible and have been found, in approximately equal numbers, in a series of 40 cases: (1) skin test positive—complement fixation negative, (2) skin test positive—complement fixation positive, (3) skin test negative—complement fixation positive, and (4) skin test negative—complement fixation negative.

Skin Test Positive—Complement Fixation Negative

Patients with positive skin tests without complement fixing antibodies have the best prognosis (table 1). In cases belonging to this group, the infection was either a recent pulmonary invasion or a localized skin involvement. The disease apparently was not extensive enough to stimulate the production of humoral antibodies in amounts sufficient to be detected by the relatively insensitive method for complement fixation.[2, 3]

The good results obtained in this group may be explained by the limited degree of infection and the excellent resistance of the patient which was aided, perhaps, to some degree by the type of specific therapy. We learned, between 1930 and 1934, that patients who had positive skin tests to a *Blastomyces* vaccine either did not improve, or actually became rapidly worse, when iodides were administered.[1] Subsequently, it has been our practice to produce partial desensitization with a *Blastomyces* vaccine before adminis-

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TABLE I

Skin Test Positive—Complement Fixation Negative

Case	Skin Test	Complement Fixation	Type of Lesion	Clinical Condition	Results
1. A. Y.	++++	0	Generalized	Good	Well—14 years
2. P. S.	++++	0	Skin—bones	Good	Well— 8 years
3. N. A.	+++	0	Skin—extensive	Good	Well—12 years
4. H. L.	+++	0	Skin—extensive	Good	Well— 5 years
5. C. A.	+++	0	Pulmonary	Good	Improved—1 yr.
6. G. D.	+++	0	Skin—lungs	Good	Well— 7 years
7. J. A.	++	0	Skin—extensive	Good	Well— 4 years
8. B. V.	++	0	Pulmonary	Good	Well— 7 years
9. F. McN.	+	0	Skin—lungs	Good	Well— 6 years
10. D. C.	+	0	Generalized	Poor	Died

tering iodides or treating local lesions with roentgen-rays. Theoretically, active immunity may have been stimulated by these small, repetitive doses of vaccine but the evidence for this is not conclusive. In some instances, the complement fixation test became positive but in other cases no detectable antibodies appeared in the serum even in patients who made a satisfactory recovery.

SKIN TEST POSITIVE—COMPLEMENT FIXATION POSITIVE

In general, the patients in this group (table 2) had more extensive infections than those in Group 1, and all had complement fixing antibodies in their serum. The treatment was the same as that employed for Group I, namely, desensitization followed by iodide therapy.[3] There were three deaths in this group in contrast to one in the first group. The course of the disease may have been influenced favorably by therapy in cases 3 and 5. The patient labeled as case 3 had pulmonary, vertebral and pelvic blastomycosis. She was desensitized, treated with roentgen-ray and iodides, and then the infected pelvic organs were removed.[4] After three years of treatment the patient made a complete recovery and was well 15 years later. It is interesting that the complement fixing antibodies disappeared from the serum following clin-

TABLE II

Skin Test Positive—Complement Fixation Positive

Case	Skin Test	Complement Fixation	Type of Lesion	Clinical Condition	Results
1. U. H.	++++	1:2	Skin	Good	Well— 4 years
2. R. R.	+++	1:2	Skin	Good	Well—10 years
3. V. S.	+++	1:16	Generalized	Good	Well—15 years
4. I. B.	++	1:8	Skin—extensive	Good	Well—1 yr.—lost
5. U. W.	++	1:2	Tibia	Good	Well— 8 years
6. W. S.	++	1:4	Generalized	Poor	Died
7. G. C.	++	1:4	Skin—bones	Good	Recent case
8. A. F.	+	1:2	Pulmonary	Good	Well—2.5 yrs.
9. W. B.	+	1:4	Generalized	Poor	Died
10. R. H.	+	1:32	Generalized	Poor	Died

ical recovery but the skin test, which had been depressed materially by the desensitization, gave a ++++ reaction 10 years after the disappearance of the complement fixing antibodies.

Skin Test Negative—Complement Fixation Positive

In this group of 10 patients (table 3) the skin tests were negative but complement fixing antibodies were present in titers ranging from 1:4 to 1:64. Physical examination revealed that all the patients had extensive generalized disease and all but two were obviously critically ill when first seen. The negative skin test is interpreted as the result of a terminal anergy analogous to that seen in patients dying of generalized tuberculosis. Martin [5] recognized this immunologic group in 1941 and emphasized the poor prognosis.

Table III

Skin Test Negative—Complement Fixation Positive

Case	Skin Test	Complement Fixation	Type of Lesion	Clinical Condition	Results
1. C. C.	0	1:64	Generalized	Poor	Died
2. E. L.	0	1:32	Generalized	Poor	Died
3. S. D.	0	1:32	Generalized	Poor	Died
4. A. Y.	0	1:16	Generalized	Poor	Died
5. W. McN.	0	1:16	Generalized	Poor	Died
6. V. P.	0	1:16	Generalized	Poor	Died
7. W. E.	0	1:16	Skin—extensive	Good	Well—4 years
8. R. M.	0	1:16	Vertebrae	Good	Well—8 years
9. J. H.	0	1:4	Brain	Good	Died
10. T. C.	0	1:5	Generalized	Poor	Died

The two patients who recovered presented a clinical picture which was quite different from those who died. One patient, presented as case 7, had hundreds of primary skin lesions scattered over the entire body, without involvement of the internal organs and made a rapid and complete recovery following intensive therapy with potassium iodide. The patient, shown as case 8, had an extensive infection of 10 ribs and six thoracic vertebrae but no invasion of other tissues. A body cast was applied to support the weakened vertebrae and iodides were administered for a period of three years. Clinical improvement began in a few months but slow progression of the destructive lesions in the bones continued for four years. The patient is in excellent health after eight years, has no local symptoms, but still wears a partial body cast because the process of recalcification is not yet complete.

The death of eight out of 10 patients with negative skin tests and high titers of complement fixing antibodies is analogous to the results reported by C. E. Smith and his associates in California for cases of coccidioidomycosis.[6] In cases of progressive histoplasmosis the same phenomenon is frequently observed, although a few patients retain their sensitivity to histoplasmin. Among the five fatal cases reported by Bunnell and Furcolow,[7] two gave positive skin tests and three were negative.

Skin Test Negative—Complement Fixation Negative

This type of immunologic response occurs in some terminal cases such as case 1, table 4, but usually the terminal cases have a high titer of complement fixing antibodies (table 3). The remaining nine patients in this group were apparently recent infections which had not yet had time to develop either hypersensitivity of the skin or complement fixing antibodies. Theoretically, if they had been allowed to evolve their disease without our meddlesome therapy, eventually they could have been classified in one or another of the first three groups.

Table IV

Skin Test Negative—Complement Fixation Negative

Case	Type of Lesion	Clinical Condition	Type of Treatment	Result
1. G. J.	Skin—generalized	Poor	K.I.	Died
2. M. M.	Lungs—lobectomy	Good	K.I.	Died
3. G. N.	Skin	Good	Vaccine—K.I.	Well—8 years
4. H. M.	Ribs—radius	Poor	Immune serum	Well—5 years
5. H. T.	Pulmonary	Good	Immune serum	Well—4 years
6. F. T.	Lungs—lobectomy	Poor	Vaccine—K.I.	Well—1 year
7. C. D.	Lungs—lobectomy	Good	Vaccine—K.I.	Recent case
8. J. T.	Lungs—lobectomy	Good	Vaccine—K.I.	Recent case
9. W. C.	Larynx	Good	Vaccine—K.I.	Recent case
10. R. B.	Larynx	Good	Vaccine	Recent case

The patient, listed as case 4, table 4, was unique and has been published in detail by Martin [8] and Jones.[9] This patient had an extensive, destructive blastomycotic lesion of the ribs and radius, was clinically ill, but had a negative skin test and no complement fixing antibodies could be detected. He evidently had an excess of *Blastomyces* antigen in his tissues since an intradermal injection of 0.1 c.c. of rabbit serum containing immune bodies produced an immediate wheal reaction. The injection of 0.1 c.c. of serum from a normal rabbit gave no reaction. After receiving a number of small doses, 0.2 to 1 c.c. of immune rabbit serum, the patient developed serum sickness but after recovery was found to have a one plus skin test to the *Blastomyces* vaccine and some complement fixing antibodies in his undiluted serum. The patient recovered and remained well for the next five years. The recovery, however, cannot be attributed entirely to the immunologic treatment since the local granulation tissue in the bone lesion of the radius was destroyed by the therapeutic application of maggots.[8] One cannot ignore entirely the effect of the serum, however, because we have seen two cases of severe moniliasis, one published [10] and one unpublished, in which there was an analogous excess of antigen in the tissues and recovery followed the use of immune serum as the sole therapeutic agent. Immune serum was employed also in the patient listed as case 5 and the therapy was followed by recovery from the original extensive pulmonary lesion.

Active Immunization with Blastomyces Vaccine

Pasteur's brilliant achievement of actively immunizing the patients with attenuated rabies virus, administered subsequent to infection but before the virus had reached the brain, has not been duplicated in any other disease. The essential requirements are: (1) a long incubation period between the time of infection and the time of dissemination and (2) a disease to which the patient can evolve a solid active immunity.

In 1941, a patient, listed as case 3, table 4, who had a rather extensive skin lesion, was treated intensively with a *Blastomyces* vaccine, roentgen-ray and potassium iodide. This patient made a satisfactory recovery and has remained well for the past eight years. It is not clear from our records why the vaccine was used and no attempt was made to ascertain if complement fixing antibodies developed subsequent to the administration of the vaccine.

In 1943, the patient, listed as case 2, table 4, was admitted to our hospital with a dense, circumscribed progressive lesion in the right upper lobe. The lobe was removed for carcinoma but the microscopic examination revealed the disease was blastomycosis. The lung was adherent to the chest wall in one area so some blastomycotic tissue was left in the chest. Large doses of potassium iodide were administered over the next six months to promote resolution and absorption of the residual lesion. The patient apparently was doing very well for six months and then developed a generalized infection of the bones and internal organs and died three months later. In reviewing this disastrous result it seemed that our therapy was ill chosen. By forcing the resolution of the granulomatous tissue with iodides, in an individual without humoral antibodies to the infecting agent, we may have accelerated unwittingly the process of dissemination.

In 1947, we studied another patient of this immunological type, case 6, where the entire lung had been removed for carcinoma in another clinic and later found to be blastomycosis. This patient had a residual lesion in one rib and a subcutaneous abscess which was discharging large numbers of *Blastomyces dermatitidis*. In this case, we attempted to immunize the patient with a heat killed vaccine made from her own organism before administering iodides.

The culture was grown on blood agar slants, suspended in physiological saline, measured by centrifugalization in a graduated centrifuge tube and then diluted with physiological saline to make a 1:1000 dilution by volume. The use of an autogenous culture is not essential since the studies of Conant, et al.[11, 12] have shown that all available strains of *Blastomyces dermatitidis* are immunologically identical.

The injections were given subcutaneously in doses of 0.2, 0.4, 0.8 and 1 c.c. every other day. The injections were discontinued for one week and then the patient's serum was examined for complement fixing antibodies. When no antibodies were found the course of the vaccine was repeated. One week after the second series of injections the serum was found to fix complement

in a 1:2 dilution. At no time were there either local or general reactions to the vaccine. If such reactions had occurred we would have interpreted them as evidence of hypersensitivity and reduced the dose of vaccine to an amount which did not produce reactions.

After the patient developed complement fixing antibodies we felt justified in starting iodide therapy. A saturated solution of potassium iodide was employed, the initial dose being 3 drops t.i.d. and the amount was increased by one drop with each dose on succeeding days until the patient was receiving 20 drops t.i.d. The amount then was reduced to 5 drops t.i.d. and built back up to 20 drops by increments of 3 drops each day. The iodide therapy was continued for six months and, in addition to the iodide, 0.5 c.c. of the vaccine was given every two weeks with the hope of maintaining or increasing the humoral immunity. A rather dramatic improvement occurred in the local lesion after the appearance of antibodies in the serum and the beginning of iodide therapy although there had been no spontaneous improvement during the previous four months. The redness and induration in the chest wall rapidly subsided and the rather copious discharge rapidly diminished until it was small in amount and intermittent in appearance.

The patient improved clinically and gained some 20 lbs. in the next two months. After four months the residual area of involvement in the chest wall was excised in another hospital and the operative wound healed without sinus formation. Three months later the patient wrote that she had gained another 10 lbs. and considered herself well. Obviously, she must be followed a number of years before she can be classified as well.

Three other cases of blastomycosis of this immunologic type are being treated by the method described for case 6 and seem to be improving.

Summary

The prognosis in patients with blastomycosis depends in part upon the extent of the infection and in part upon the immunologic response of the patient.

The prognosis is best in patients who have positive skin tests and no demonstrable antibodies in their serum (table 6). The prognosis is poorest in

Table V

Results by Immunologic Groups

Group	Recent Case	Lost	Well	Died
1. Skin test positive—complement fixation negative	1	0	8	1
2. Skin test positive—complement fixation positive	1	1	5	3
3. Skin test negative—complement fixation positive	0	0	2	8
4. Skin test negative—complement fixation negative	4	0	4	2
Total	6	1	19	14

those with negative skin tests and a high titer of complement fixing antibodies in their serum.

Patients having positive skin tests should be desensitized before being treated with iodides regardless of the presence or absence of antibodies.

Patients with neither positive skin tests nor complement fixing antibodies should be actively immunized with a heat killed vaccine made from the yeast phase of *Blastomyces dermatitidis* before being treated with iodides.

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SUPERIOR VENA CAVA OBSTRUCTION IN PRIMARY CANCER OF THE LUNG *

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Obstruction of the superior vena cava as a complication of primary cancer of the lung has not been adequately studied. References to this association in the literature are infrequent. Although a case of superior vena cava obstruction secondary to primary lung cancer was reported by Barth [1] as early as 1853, Brown [2] was able to collect only 39 such cases from the world literature up to 1930. Since then, only a few clinical and pathological reports on this condition have appeared.

This report is an analysis of eight instances of superior vena cava obstruction occurring among cases of primary lung cancer seen in recent years at the Veterans Administration Hospital, Aspinwall, Pennsylvania. Seven cases were diagnosed as bronchogenic carcinoma by bronchoscopic or lymph node biopsy or at autopsy. The eighth case clinically appeared to be an unquestionable instance of bronchogenic carcinoma, but histologic proof was not available.

A tabular analysis of certain clinical and pathological features is presented in table 1.

As patients admitted to this hospital are almost without exception males, all cases were of that sex. All were white. The youngest patient was 42 years. The others ranged from 48 to 59.

The interval between the first manifestations of pulmonary disease and the development of the superior vena cava syndrome varied widely, and ranged from 10 to 20 months in four cases. Three others were ill only three to six weeks before superior vena cava obstruction occurred, and the eighth patient developed obstruction before symptoms of pulmonary disease appeared.

Seven of the eight cases died three to 10 weeks after the onset of manifestations of superior vena cava obstruction. The eighth patient is alive and in the hospital 12 weeks after obstruction developed. He has been given a course of nitrogen mustard and at present is receiving roentgen-ray radiation. There has been slight clinical improvement.

The onset of symptoms was characteristic and striking in all patients. There was initial venous distention followed by the appearance of swelling of the face, neck, shoulders, and arms. In addition, the onset was marked by sudden increase of preëxisting dyspnea (three patients), facial cyanosis (one

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TABLE I

Case	Age	Illness Prior to SVCO*	Survival After SVCO*	Origin of Tumor	Method of Diagnosis	Microscopic Diagnosis
1	50	6 weeks	6 weeks	Rt. main bronchus	Autopsy	Squamous cell, grade IV
2	55	20 mos.	6 weeks	Rt. main bronchus	Autopsy	Completely undiff. (oat cell)
3	59	None	7 weeks	Rt. upper lobe	Biopsy cervical node	Completely undiff. (oat cell)
4	51	3 weeks	10 weeks	Rt. main bronchus	Bronchoscopic biopsy	Squamous cell, grade III
5	56	10 mos.	3 weeks	Rt. upper lobe	Biopsy cervical node	Undiff., grade IV
6	56	13 mos.	5.5 weeks	Rt. main bronchus	Bronchoscopic biopsy	Biopsy inadequate
7	48	10 mos.	3.5 weeks	Rt. main bronchus	Biopsy cervical node	Squamous cell, grade IV
8	42	3 weeks	12 weeks (living)	Rt. upper lobe	Biopsy cervical node	Moderately undiff.

* Superior vena cava obstruction.

FIG. 1. Superior vena cava obstruction with edema of face, neck, chest, arms, and hands, and showing a plexus of venules across the lower chest.

patient), and headache (one patient). Eventually cyanosis appeared in all but one case. Similarly, seven of the eight patients became intensely dyspneic.

All patients developed dilated, distended veins on the forehead, neck, shoulders, arms, chest, and abdominal wall. In two cases there was dilatation of smaller caliber vessels along the lateral chest wall and back with venous distention on the lower abdominal wall.

There was marked progression of all symptoms until death. Frank pitting edema of the forearms appeared in four patients. Two of these had grossly edematous hands which were painful (figure 1).

FIG. 2. Gross specimen showing the superior vena cava completely surrounded by bronchogenic carcinoma with its lumen occluded by invading polypoid tumor masses.

In six cases, intensification of the cyanosis, dyspnea, and venous distention occurred in recumbency. Conversely, these patients felt better when sitting up.

Roentgen-ray examination of the chest revealed no characteristic picture. Two patients, however, displayed a widened superior mediastinal density compatible with a dilated superior vena cava. Phlebograms, obtained in two cases, revealed extensive collateral circulation, but the contrast medium failed to reveal the site of superior vena cava obstruction. Electrocardiographic findings were not significant.

FIG. 3. Phlebogram revealing extensive collateral circulation.

The primary lesion was in the right upper lung in all patients, and in four of these could be demonstrated in the right main bronchus.

The following pathologic findings were demonstrated in one of the autopsied cases:

A large firm tumor mass which originated in the right main bronchus filled the superior mediastinum. The azygos vein was obliterated, the su-

perior vena cava compressed, and its lumen was completely occluded by invading tumor tissue which took the form of dangling, multiple, polypoid masses (figure 2).

The following brief case history represents a typical picture of the development of superior vena cava obstruction complicating bronchogenic carcinoma:

A 51 year old, white coal miner was brought to the hospital by ambulance because of progressive weakness, dyspnea, and cough with hemoptysis, of six weeks' duration. Three weeks after onset, he developed swelling of the face, neck, and right arm. On admission, he appeared acutely ill, mentally confused, orthopneic, and cyanotic. The face, neck, and right arm were edematous, and small dilated venules were present along the right anterior chest wall. Venous pressure was over 300 mm. of water in the arms and normal in the lower extremities. Roentgen-ray film of the chest revealed a density in the right upper lobe and a widened superior vena caval shadow. A venogram revealed extensive collateral circulation of the right arm and hemithorax, but the superior vena cava was not demonstrated (figure 3). Bronchoscopic biopsy, taken from a large fungating mass in the right main bronchus, revealed squamous cell carcinoma, grade III. His condition grew progressively worse, he developed pulmonary edema, and died five weeks after admission.

Discussion

Primary cancer of the lung may produce obstruction of the superior vena cava by three mechanisms: (1) intraluminal obliteration; (2) external compression; (3) thrombosis by external compression or invasion of vein by tumor cells. Two of our autopsied cases revealed the superior vena cava to be obstructed by a combination of all three mechanisms. Fischer [3] found invasion of the caval wall in 10 instances of a series of 18 collected cases of superior vena cava obstruction due to primary lung cancer. Jaffe,[4] in an analysis of 100 autopsied cases of carcinoma of the lung, discovered invasion and obliteration of the superior vena cava by the tumor in seven.

It is noted that the tumor originated in the upper right lung in all of our cases. Dana and McIntosh [5] similarly noted this location of the tumor in cases involving the superior vena cava, and suggested that carcinoma which arises in the left lung is more apt to result in death before extension to the superior vena cava can take place.

The occurrence of superior vena cava obstruction in relation to other causes should be considered. Brown,[2] in a summary of some 300 cases of superior vena cava obstruction, estimated that about 27 per cent were due to aortic aneurysm and an equal number to mediastinal tumor. In 25 per cent of his cases the obstruction was due to carcinoma of the lung, bronchi, and adjacent organs. The remaining 20 per cent were ascribed to various, infrequently observed causes.

Regardless of the cause, obstruction of the superior vena cava results in a characteristic syndrome. The superior vena cava drains the upper half of the body, including the head, neck, arms, chest, and upper abdominal wall.

The signs and symptoms which develop following impairment of the venous return from this area vary with the degree of obstruction and with the presence or absence of occlusion of the azygos vein. Ochsner and Dixon [6] consider the following signs as pathognomonic of the superior vena cava syndrome:

(1) Edema and cyanosis of the face, neck, and upper extremities
   a. Aggravated by assuming the horizontal position
   b. Relieved when erect
(2) Venous hypertension in the arms
(3) Normal venous pressure in the lower extremities
(4) Development of subsequent varicosities of the anterior thorax

It is important to realize that the onset of superior vena cava obstruction may be the first manifestation of primary cancer of the lung. One of our patients experienced no symptoms referable to the respiratory system before the appearance of manifestations of superior vena cava obstruction. Early in the course, symptoms are likely to be slight, because of the development of a collateral circulation. Edema develops as the obstruction progresses. Edema of the eyelids may be an early sign of the syndrome.[7] Rauth [8] reported a fatality due to severe edema of the larynx.

Cyanosis is first observed in the lips and ear lobes and tends to progress. It is due to decreased oxygenation of tissues as a result of venous congestion.[9]

Dyspnea is a prominent symptom, occurs early, and may be attributed to retarded blood flow leading to venous stasis in the brain. Orthopnea, hyperventilation, paroxysmal dyspnea, or periodic breathing may also occur for the same reason.[10] Patients with preëxisting dyspnea due to the underlying bronchogenic carcinoma may exhibit a sudden increase of dyspnea with the appearance of superior vena cava obstruction. Cerebral symptoms, such as headache, fullness in the head and ears, dizziness, drowsiness, and mental lethargy are explained as due to dilatation of the cerebral veins with increased intracranial pressure and chronic congestion of the cerebral tissues.[9] The development of Jacksonian epilepsy in these patients has been noted.[7] The cerebrospinal fluid pressure may be increased,[11] as was demonstrated in one of our cases. Conjunctival suffusion and prominent, staring eyes may occur from increased cerebral pressure.[12] The fundal veins are likely to be distended.

Characteristically, most of the signs and symptoms are aggravated in recumbency as a result of increased venous stasis in this position.

As mentioned previously, the elevated venous pressure is manifested by dilated veins of the head, neck, chest, and arms. Small superficial groups of dilated venules may appear along the anterior costochondral margins and be the first evidence of superior vena cava obstruction. Their presence is an indication for a thorough examination of the chest.[13] As the collateral circulation becomes more extensive, venous distention appears in the lateral and posterior chest wall, and the upper and lower abdominal wall.

The collateral channels which develop following obstruction of the superior vena cava have been adequately described by Carlson.[14] Experimenting with dogs, he demonstrated that following obstruction of the superior vena cava alone, the blood is shunted to the azygos system and returned to the heart. With blockage of the superior vena cava and the azygos vein, all of the blood returns from the upper half of the body through the inferior vena cava.

Obstruction of the superior vena cava including the azygos vein is of course more serious and possibly may be determined clinically. Such obstruction may be marked by the appearance of large veins in the lower abdominal wall and groin. Reversal of blood flow may be demonstrated as the veins fill from above downward.[7] Another method for demonstrating obstruction below the azygos vein is to note the oscillating effect of respiration on the column of saline in a tube placed in an arm vein.[15] Complete obstruction below the azygos vein causes the column to rise with inspiration and fall with expiration. Normally, the opposite effect is observed. This paradoxical pulsation is evidence that the venous shunt is via the inferior vena cava and suggests blocking of the azygos vein. Obstruction below the azygos vein may also be demonstrated by blocking, by means of a constricting band about the chest, the superficial chest veins carrying blood to the inferior vena cava.[15] Obstruction above the azygos vein will not result in increased venous pressure in the arm as the blood is shunted via the superficial thoracic veins into the azygos system. In addition, Veal and Hussey [16] have pointed out the value of an exercise test to differentiate local from general causes of elevated venous pressure. The venous pressure response to repeated clenching of the fist for one minute is marked in patients with obstruction anywhere from the axillary vein to the superior vena cava. Such exercise is without effect in cardiac patients.

Only a few laboratory examinations are of value in the diagnosis of superior vena cava obstruction. The venous pressure is always markedly elevated in the upper extremities and is within normal limits when taken in the femoral veins. Frequently, arm to tongue circulation time is not so prolonged as might be expected from the height of the venous pressure. Recently the value of phlebography for localization of the site of obstruction has been demonstrated.[17]

The appearance of superior vena cava obstruction secondary to primary cancer of the lung is an ominous occurrence. From a study of our patients, death may be expected in three to 10 weeks in untreated cases. Ferris and Williams,[18] however, reported a case of bronchogenic carcinoma in which death occurred six months after the onset of superior vena cava obstruction.

Treatment is of course symptomatic. Some relief of venous pressure may be obtained by draining 100 c.c. to 150 c.c. of blood at proper intervals. The usual methods of treatment of carcinoma of the lung may be of value, but the presence of superior vena cava obstruction indicates that the patient is inoperable.

Summary

An analysis, together with a discussion of the findings, of eight cases of superior vena cava obstruction occurring as a complication of primary cancer of the lung has been presented. In all instances, the tumor originated in the right upper lobe. In seven of the eight cases, death occurred three to 10 weeks after the onset of obstructive manifestations.

Obstruction of the superior vena cava is an important and not infrequent complication of bronchogenic carcinoma and may be the first indication of this disease. The development of this complication is an ominous occurrence.

Addenda

Case 8 died 14 weeks after the onset of symptoms of superior vena cava obstruction. Autopsy disclosed a tumor originating in the right main bronchus which invaded the wall of the superior vena cava, completely occluding its lumen, from the auricle to the subclavian vein. The azygos vein was similarly compressed.

Since the completion of the above report an additional case of superior vena cava syndrome secondary to bronchogenic carcinoma has been observed. The patient was ill 10 weeks before the obstruction manifested itself. Death occurred five weeks later. Figure 4 clearly illustrates the extensive collateral circulation over the chest and abdomen which developed following obstruction. In contrast to the other eight cases, the

Fig. 4. Infra-red photograph taken four weeks after onset of superior vena cava obstruction demonstrating extensive collateral circulation over chest and abdomen.

carcinoma originated in the left upper lobe. Autopsy revealed extension of the neoplasm into the mediastinum with infiltration of the wall of the superior vena cava and compression of its lumen. The tumor was classified as undifferentiated bronchogenic carcinoma (oat cell) by microscopic examination.

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THE INCIDENCE OF HYPERTENSION IN PORTAL CIRRHOSIS: A STUDY OF 80 NECROPSIED CASES OF PORTAL CIRRHOSIS *

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It is the general impression of many physicians that hypertension occurs much less frequently in patients with portal cirrhosis than in the general population. This impression receives some support from the statement in Oxford Medicine [1] that "in portal cirrhosis, the pulse is slightly quickened, the blood pressure, both arterial and venous, usually is low," and the statement in the book by Rolleston and McNee [2] that "the blood pressure is low when the disease is active." However, there are not many references in the literature dealing specifically with the subject of hypertension in portal cirrhosis.

In 1943, Kirshbaum and Shure [3] stated, "There seems to be no indication that cirrhosis of the liver, per se, has any marked effect on the cardiovascular system." Another report by Bouchut et al. [4] resulted in similar conclusions.

There is no mention in these reports of the incidence of hypertension in the general population to which its incidence in portal cirrhosis must be compared. Moreover, the standards used for the diagnosis of portal cirrhosis in these studies were not mentioned and thus may differ from each other and from those used in the present series.

In view of the above, it seemed pertinent to investigate the incidence of hypertension in autopsied cases of portal cirrhosis at this hospital.

In an effort to standardize the cases used in this series and to prevent possible disagreement on the amount of microscopic pathology needed to establish the diagnosis of portal cirrhosis, all cases which did not show nodules or a "hob-nail" appearance grossly were discarded. Microscopically these cases also showed markedly increased periportal fibrosis, cellular infiltration of the periportal connective tissue, disorganization of liver lobules with disappearance or dislocation of central veins, regeneration of hepatic cells and an apparent increase in the number of bile ducts.

The first problem was to arrive at some conclusion as to the incidence of hypertension in the general population. This was difficult because of the different standards and various population and age groups used by various investigators. Some of these are given below.

Master et al.[5] studied 15,000 men and women over 40 years of age. Using various standards for hypertension, such as 140/90, 150/90 and 150/100 mm. Hg, the authors found hypertension present in a surprisingly large portion of the general population. For example, if 140/90 mm. Hg is

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the upper limit of normal, practically one-half the male population and 60 per cent of the females over 40 years of age may be considered hypertensive. In fact, these workers find the high values so common that they feel the upper limit of normal blood pressure may be above 150/100 mm. Hg.

Robinson and Brucer,[6] in a study of 10,883 persons 20 to 70 years of age, found that the normal range of systolic blood pressure is 90 to 120 mm. Hg and the diastolic 60 to 80 mm. Hg. They felt that 40 per cent of the adult population is either actually or incipiently hypertensive.

Wilbourne and Ceccolini[7] in a study of 25,000 men aged 18 to 45 years, using 150/90 mm. Hg (army standard) as the upper limit of normal, found the incidence of hypertension to be only 0.96 per cent. It is interesting to note that in the first blood pressure determination in each individual of this group, 18 to 20 per cent had a systolic tension over 140 mm. Hg. The probable reasons for the low readings in this series are the youth of the subjects and the fact that those with initial readings of over 150/90 mm. Hg were required to rest for long periods to bring down their pressure to acceptable limits for army service. Bell[8] stated that if 140/90 mm. Hg is the upper limit of normal then nearly half the population over 50 years of age has hypertension in some degree.

Daley et al.[9] concluded that a blood pressure above 140/90 mm. Hg is abnormal at any age.

It was Fishberg's[10] opinion that a systolic pressure above 150 mm. Hg is to be regarded as abnormal at all ages, as is a diastolic pressure above 90 mm. Hg.

The book, "Nomenclature and Criteria for Diagnosis of Diseases of the Heart,"[11] put out by the American Heart Association, defines 140/90 mm. Hg as the upper limit of normal blood pressure.

After some deliberation, we decided to use 140/90 mm. Hg as the upper limit of normal, particularly because it is the standard used by the American Heart Association and it is commonly accepted in the literature. In this series, the patient was considered hypertensive if either the systolic or the diastolic pressures were elevated above their respective standards.

In our series of 80 cases of portal cirrhosis, all the patients were hospitalized and most of them were in-bed patients. The mean of at least four readings taken at different times was used as the actual blood pressure value. Five cases were rejected because the only recorded pressures were terminal in nature and these were all low. One was discarded because of the existence of aortic insufficiency, one because of bilateral suppurative nephritis and one because of glomerulonephritis.

Thus 72 cases were used in the actual computations. Of this group, 40 were males and 32 were females. Fifty-five of the patients were between 41 and 70 years of age. There were 12 cases in which the systolic pressure was above 140 mm. Hg, the diastolic pressure above 90 mm. Hg, or both levels were elevated. Thus 17 per cent of all the patients had hypertension. However, these figures include patients below 40 years of age among whom

there was only one case of hypertension, so that among 60 cirrhotics above 40 years of age, there were 11 cases of hypertension (18 per cent).

In the table below the incidence of hypertension in the general population above 40 years of age as determined by Master et al. [5] is compared with that in the present series.

From the above table it may be seen that the incidence of hypertension is markedly less in our series. It may also be seen that the increasing incidence of hypertension with age occurs in our series as well as the other. The possible explanations of the difference in incidence of hypertension in the two groups will be discussed later.

If the weight of the heart is to be used as a criterion of hypertension, we have some difficulty again in establishing a standard. The generally accepted upper limit of normal weight of the heart is 300 gm. in females and 350 gm.

TABLE I

	Patients with hypertension in general population (Master et al.[5])			Patients with hypertension in the present series of portal cirrhosis (Spatt and Rosenblatt)
	Male	Female	Total*	Total
Age 40 and over	49.8%	59.8%	Over 50%	18%
Age 50 and over	59.9%	72.5%	Over 60%	21%
Age 60 and over	70.5%	79.6%	Over 70%	28%
Age 70 and over	77.3%	82.2%	Over 78%	45%

* The figures in the total column are approximate and were not mentioned by Master et al. They are used here to compare with our total figures since we do not have enough cases to make a separate tabulation of males and females in a statistically significant manner.

in males. However, Bell [8] has written concerning the difficulty in using heart weights as the basis for the diagnosis of hypertension since the weight of the heart varies with the muscular development and weight of the individual. He also stated, "One might expect the weight of the heart to correspond to the intensity of the hypertension, but this is often not the case." As for the actual heart weights, he found that a heart weighing 350 gm. in females and one weighing 400 gm. in males is strongly suggestive of hypertension. Weights of 450 and 500 gm., respectively, nearly always represented hypertensive disease.

Thus, if the lower standards of heart weight are used (300 gm. for females and 350 gm. for males), 35 per cent of the patients in our series had hypertension. If the higher standards are used (350 gm. for females and 400 gm. for males), 25 per cent had hypertension.

In order to compare the weights of the hearts in our series with those in a group of unselected cases, we used 300 autopsy cases from the files of this hospital. These cases were unselected except as to age, all being over 21 years of age (table 2).

The markedly lower incidence of hearts above normal weight in the cirrhotic group seen in table 2 seems to agree with lower blood pressure readings in this group as contrasted with the general population.

After carefully analyzing the 12 cases in our series which did show hypertension, no consistent clinical difference from the non-hypertensive cases was found (except for the presence of hypertension and a history of hypertension). Some of the factors reviewed were sex, age, alcoholism, jaundice, ascites, and arteriosclerosis.

TABLE II

Comparison of Heart Weights

	Per Cent of Hearts Above Upper Limits of Normal Weight	
	Standards: 300 gm. for females 350 gm. for males	Standards: 350 gm. for females 400 gm. for males
300 unselected cases (over 21 years of age)	65%	48%
69 cases of portal cirrhosis (over 21 years of age)	36%	26%

The only fairly consistent pathological difference between the hypertensive and non-hypertensive groups was the weight of the heart. This was greater in most of the hypertensive group.

DISCUSSION

A portion of the difference in incidence of hypertension in our series from that of Master et al.[5] is probably due to differences in the technic of taking the blood pressures. Obviously, the patients in our series were quite ill, since they died at the end of their hospital admissions. Therefore, they were in bed during the blood pressure determinations and probably had been in bed for many days successively before these determinations were performed. This factor would tend to lower their blood pressures to some extent as shown by Wilbourne and Ceccolini.[7]

It is interesting to speculate on the other possible reasons for the lower incidence of hypertension in cirrhotic patients.

It is possible to postulate a hypothetical substance which is produced by the cirrhotic liver which causes arteriolar dilatation. This substance may be related to bile salts which are thought [2, 13, 14] to have a hypotensive effect. There is no definite evidence that some product of the cirrhotic liver accumulates in the blood and causes a lowered blood pressure. Nor is there any evidence to support the theory that some product of the cirrhotic liver acts on the myocardium in such a way as to induce a lowered tension. Although the statement was made by Rolleston and McNee [2] that the low tension is a toxic effect, they presented no data to support their statement.

A more likely cause of hypotensive tendencies in cirrhotic patients is the generally poor nutritional status of these people. It is thought by some that the beneficial effects of the Kempner [12] rice diet in hypertension is due mainly to a similar effect.

The speculation above, however, is not supported by any factual data at present, so that the lower incidence of hypertension in patients with portal cirrhosis is largely unexplained.

It is realized that definite conclusions of any significance cannot be drawn from this small series. For this reason, it is hoped that the statistics in other hospitals will be evaluated in an effort to clarify this point. Furthermore, if it is found by others that portal cirrhosis and hypertension appear mutually antagonistic, a new approach to the etiology and therapy of the latter may be indicated.

Conclusions

The incidence of hypertension in patients with portal cirrhosis is significantly lower than in the general population, using blood pressure readings, heart weights or both, as criteria.

The lower incidence of hypertension in patients with portal cirrhosis is unexplained at the present time.

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ON THE CLINICAL ENTITY *

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THE object of this paper is to identify certain dimly-conscious thought processes gone through every day by physicians and to emphasize the significance of some of them, but it does not claim to contain anything new. More specifically, we are here discussing factors a physician observes and reflections he makes to comprehend a group of patients as similar, or to visualize an individual patient in his totality. The result of the former comprehension will be called a clinical entity. (That of the latter is named individual diagnosis.)

Since the term clinical entity denotes a concept of uniformity in patients, the concepts of clinical entity and of disease may have identical outlines. However, the term clinical entity as here used characterizes a practitioner's concept, i.e., centers around therapeutic or preventive measures. It, therefore, implies healthy as well as disease states and may furthermore differ from that of the disease entity whenever the latter does not imply the uniformity a physician needs. For instance, the exudative and productive forms of tuberculosis of the lung are differentiated as clinical entities, while on the other hand, scarlet fever and streptococcal sore throat may soon be considered a single entity. Also, the term disease is often used ambiguously by workers in different branches of medicine, and since its meaning has altered in the course of medical history, it seems practical to adopt the term clinical entity to denote a precise interpretation.

The introduction of the paper (Part I) will deal with reasons why the task is being undertaken. Part II will outline the concept of the clinical entity, enumerate the factors that make up this constellation, and comment on these factors. Part III will point out some practical conclusions to be drawn from a clear understanding of the clinical entity for teaching, research and practice in the field of medicine.

I

The clinical entity is the ultimate reference for the entire field of medicine: as Knud Faber [1] expresses it in his outstanding monograph, *Nosography, The Evolution of Clinical Medicine in Modern Times*, ". . . the physician cannot live, cannot speak, cannot act without it." Yet, despite this central position which the clinical entity apparently holds in medical thinking, it is a singular fact that since the first edition of Sir Thomas Clifford Allbutt's *System of Medicine* in 1898 [2] little attention other than Knud Faber's work has been paid to answering the question of what factors constitute a clinical

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entity, or, to express it as would the practicing physician, "When can an actual patient be considered sufficiently examined?" Officially recommended textbooks of medicine [9] omit the subject: without a general introduction, these books begin immediately with chapters in which special topics are discussed. Barker, Christian, and Sir James Mackenzie,[12] in their respective chapters of *Oxford Medicine*, mention it, but not one makes the subject a focal point of discussion. *The Standard Nomenclature of Disease* (*Standard Classified Nomenclature of Disease*) [14] outlines briefly a concept of the disease entity (clinical entity) in its editions of 1933 and 1935, but not in that of 1942. It defines this entity as follows: "Each disease entity is made up of two components: the site and the etiological factor." This characterization of a particular disease has proved its value for cataloguing purposes. However, for a practicing physician or medical research worker, the principle needs to be expanded.

Such a state of affairs in regard to the concept of the clinical entity is unfortunate. It retards the growth of medicine (i.e., of course, clinical medicine—therapeutic or preventive) as a genuine natural science—a most undesirable situation for both patient and physician. Without textbook reference to how medicine arranges its thoughts in general, but with textbook accent solely on "special diseases," the student, particularly the undergraduate one, is easily led to the diagnosis of labels rather than processes, to fit the patient to the cloth rather than the cloth to the patient. He easily falls victim to routine and habit—a temptation difficult to avoid under any circumstances—and may be inclined to consider today's and yesterday's clinical entities as final. He is apt to forget the continuous development of nosography, the fact that at different periods in medical history identical terms express different concepts (e.g., the interstitial nephritis of Bartels and that of Volhard) and different terms similar concepts (e.g., nephrosis and tubular nephritis). He thus loses an insight valuable in deepening his professional understanding that we are in medicine, as elsewhere, not only creators, but also creatures.

Furthermore, this lack of textbook reference produces an intellectual and emotional breach in medical education. Preclinically, the student is taught and trained rigidly to reduce the multiformity of his observations in a given field to a common denominator, e.g., the atom in physics and chemistry, the cell in biology, and the function in physiology. Clinically, he finds an obvious incongruity of denomination; in one instance a topographical designation, such as diseases of the cardiovascular system, in another an etiological one, such as infectious diseases, and in still another a physiological designation, such as diseases of metabolism, etc. The novice at the bedside is thus disillusioned and confused to find so little reference to what seemed to be the core of endeavor in the forefield of his clinical education.

The task of the medical laboratory worker would also be balanced by recognition of the clinical entity. Retired from the natural panorama of events in order to concentrate his attention upon a particular set of signs, the

medical pharmacologist or physiologist is not always aware of the multiformity of pathological phenomena in the clinician's field of vision and the problem of their arrangement. He is thus in danger of losing in depth and breadth what he has gained in focus. Only consciousness of and familiarity with the concept of the clinical entity will fruitfully guide the pathogenic explanations and therapeutic or prophylactic suggestions he submits to the physician.

Moreover, lack of reference to the concept of the clinical entity misrepresents the diagnostic portion of medicine to those medical research workers who are predominantly trained in classical physics and chemistry. Such workers are accustomed to consider their subjects of study as entirely materialized in, or exchangeable with, their standard of reference. In chemical analysis, the ultimate products are identical with one element or a combination of elements of the periodic system. A "type" * (such as the "steroid group" or the "biological amine group"), a standard of a higher order than the subject under study, integrating several independent solitary characteristics into an individualized unit, plays only a transient rôle in the identification of a chemical compound. Such workers are therefore understandably inclined to transfer this attitude of relation between materials to be analyzed and atoms to the relation between patients and diseases. In medicine (and biology), however, it is types that form the background of identification. The single patient is a representative of, but not a replica of, a disease complex.

Finally, although tremendous progress has been made and will continue, in the field of understanding numerous isolated pathological phenomena by applying the classical physico-chemical point of view, clinicians may be unduly impressed by it in the realms outside its jurisdiction. Probably a tendency to undue exactness of identification is the main reason for the abovementioned neglect of the concept of the clinical entity in general. Today's situation is perhaps somewhat similar to that which existed 100 years ago when Virchow [16] alluded in the opening article of his *Archiv* to the "invasion of chemistry in the field of medicine" and to the "devastation" it had produced. Apparently he referred to the iatro-chemical and iatro-physical period in the history of medicine in which all phenomena of life were held to be understandable on the basis of physico-chemical principles. However, the modern atom concept, which characterizes even single atoms of the same element as unique units rather than exact duplicates will certainly tend to alleviate today's danger.

II

The clinical entity is a concept that has been created and is perpetuated by physicians to facilitate diagnostic and therapeutic approaches to the individual patient. It is a technical tool to delineate among the bewildering

* The word *type* is here used in its medical definition: "The usual form, or a composite form, which all others of a class resemble more or less closely; a model; noting especially a disease or a symptom-complex giving the stamp or characteristic to a class." [6]

mass of phenomena encountered in human pathology some significant arrangement of events. The basis for delineation and the actual sets of phenomena that constitute such an arrangement vary at different historical periods.

Physicians, of course, have developed numerous theories concerning the nature of disease, but medical historians tell us that dissenters in theory have often agreed on practical approach to individual patients.[11, 12] It is the clinical entity which bridges the gap between these different theories. Being predominantly a technical tool, it is relatively far removed from the background of theoretical speculation. Cultural differences in the disease concept,[1] however, are not eliminated.

The clinical entity plays different rôles in research and practice: the research clinician is concerned with its development, while the practicing physician is concerned with its application. The former uses single individuals as material to visualize a clinical entity; the latter, on the other hand, uses single clinical entities as material to visualize the individual. The former uses other entities as his standard of comparison, while the latter in final analysis must find his "norm" * in the patient himself. The creative action of the practicing physician lies in ultimate visualization of the patient as unique and individual (individual diagnosis), despite the necessity of classification as an introductory step.

The general question of individuality leads to consideration of two points of view for biological dynamics—one related to arbitrary repeatable ranges of time (today's experiment will be repeated tomorrow, or, on a larger scale of observation in time, we accept the concept of "eternal laws" in nature),

* It is important to differentiate the concepts of *mean, classical type,* and *norm.*[8, 10] There are two methods of seeing several single variable units as one: *averaging* and *typing.* In the former, single objects under study are measured and the frequency of some is the decisive factor in determining the general unit: the single objects agglomerate around this center in diminishing order. *Mean* is the designation for the kind of general unit obtained by this method. In typing, one views the single objects as non-measurable, individual wholes, and some visualized ideal is the common denominator; the single objects comprehend this ideal in varying degree. *Classical type* is the designation for the kind of general unit obtained by this method.

Norm (in biology) is the term used to characterize the actual content of a general unit obtained by either of these two methods. Therefore, depending upon the approach chosen, there are two kinds of biological norm: the *frequency norm* and the *ideal norm.* These may, of course, closely approximate each other.

The characteristics of the method of averaging and of the frequency norm (statistics) are more widely understood than are the principles of the method of typing and of the ideal norm. Since visualization and not frequency plays the decisive rôle in the method of typing, the manifestation of a first and only patient may be sufficient to envision a new classical type, a new clinical entity. Similarly, the ideal norm can refer not only to a group of persons, but to a single one; as outlined in Grote's concept of responsivity, one may visualize the potentiality of a person in comparison to his actuality. Although the classical type and the ideal norm are not derived by calculation, as are the mean and the frequency norm, there is nothing more mystic about them than about any other concept that concerns individuality.

If the subject of reference of the several single units is not variable or if its variability is considered insignificant, no particular term for the general unit is necessary, but the whole group receives a designation, as for instance, *species,* family, etc. In clinical medicine a group of persons exposed to any microörganism or to any drug might be designated as a species. Again, ideal norm and frequency norm may approximate each other.

A discussion of the clinical entity as related to these categories will not be undertaken here.

the other related to the uniqueness of time, the continuous flow of time in the historic sense (today never returns—tomorrow comes only once, "time marches on"). A detailed philosophical discussion about this differentiation, to what extent these two attitudes can, from a certain standpoint, be viewed as one, is beyond the scope of this paper. However, in the present state of our knowledge, a clear recognition of the differences in these points of view is useful to the physician. Standards of functional tests or therapeutic activity are based on acceptance of "eternal laws" set up by repeated experience—the "science" of medicine. On the other hand, transformation of manifestations of one individual or several into a single, specific, ideal unit (clinical entity) is predominantly based, similar to the activity of an artist, on the view of dynamics in the historic sense—the "art" of medicine. The concept of individuality is exclusively recognized from the historic point of view.

There remains one final historical-philological problem to be considered before we may properly delineate the concept of the clinical entity. It is the use of the word *entity*. Clendening and Hashinger [4] in the 1947 edition of *Methods of Diagnosis* quote at length Sir Thomas Clifford Allbutt's rejection of that term. Sir Clifford bases his rejection mainly on the historical viewpoint (as he bases his rejection of the term type in a similar manner) that ". . . it was born to signify that reality of substance which was once supposed to underlie abstract names, and in these ontological circles it has moved ever since." It is obvious from all that has been said here that the term *entity* as used in this paper is not understood to denote a disease as concrete, but only to indicate uniformity. In this sense the term *entity* is well entrenched in today's medical vocabulary and it, therefore, seems justified to continue to use it.

Having clarified certain relationships of the clinical entity, we shall now discuss its content. For practical purposes its constituents are listed under five headings, with parenthetical reference to textbook usage:

I. The Zoölogic-Constitutional Factor
(i.e., human constitutional variations)
II. The Environmental (etiologic) Factor
(e.g., infectious diseases)
III. The Topographic Factor
(e.g., diseases of the cardiovascular system)
IV. The Pathologic-Morphologic Factor
(e.g., tumor, degeneration, etc.)
V. The Pathologic-Physiologic Factor
(e.g., diseases of metabolism)

I. *The Zoölogic-Constitutional Factor.* The human organism as a whole, as an individual, is the initial and ultimate subject of all our medical efforts, and, aside from questions of metaphysical attitude, its outstanding characteristic for the physician is aging and dying. His standards for "nor-

mal" depend on the patient's age and the irreversibly finite course of life. No other characteristic of the human organism among those mentioned in the biological textbooks needs to be emphasized more to the physician today. Current standard textbooks of physiology do not list the subject of death in their indices, nor is it easy to find a broad and thorough systematic discussion about death from the standpoint of its natural inevitability. However, it is apparent that the phenomenon of physiological death is implied in any concept of at least multicellular life.

Since the days of Hippocrates it has been recognized that the establishment of a normal life-span for all men is too broad for the physician, and the usefulness of subdividing *Homo sapiens* into types of different constitutions, beginning with the obvious sex differentiation, has long been accepted as necessary.

II and III. *The Environmental (Etiologic) and the Topographic Factors.* These two factors help to set the scene for the pathologic-physiologic and the pathologic-morphologic to which the clinical entity and comprehension of the individual patient must ultimately refer.

The *environmental* factor is relatively uncomplicated in analysis. It is simply subdivided into specific and non-specific headings: *conditio sine qua non*, such as infectious and deficiency diseases; and *conditio sine qua etiam*, such as climatic and social factors. Epidemic occurrence, as such, is no longer considered a separate subheading of the environmental factor but rather a combination of a number of factors of the clinical entity.

Literally interpreted, *topographic* factor means a site of involvement. However, it is, of course, not merely the point at which pathologic manifestations appear, but rather the central point of disorder, the prime one from the standpoint of causal relationship (be it mechanical or psychogenic), or a nodal one from the teleologic standpoint. This prime or nodal point may shift during the course of events, resulting in a new entity: for instance, when the pneumonia has been successfully treated, if a secondary empyema remains, the topographic factor of the disease has changed.

Interest and discussion concerning the topographic factor center today around the psychosomatic differentiation and relationship of the organism. It is particularly interesting that a recent investigation [17] suggests a new teleologic perspective regarding the relationship between psychic and somatic disturbances: somatic disease as cure rather than sign of conversion or repression of an unsolved psychic conflict.*

IV and V. *The Pathologic-Morphologic and the Pathologic-Physiologic Factors.* These factors are closely related, since both structure and function reveal the well or ill being of the organism. Today their close and significant relationship is somewhat underrated in favor of the differences existing between them.

* The "center" concept versus the "organismic" concept of the structure and function of the central nervous system [7] is a physiologic rather than a topographic problem, but in any event beyond the range of this paper.

Matter and motion, or structure and function, as we call matter and motion when viewed in relation to a whole, are two fundamental concepts of all the natural sciences. The three factors of the clinical entity so far mentioned (the zoölogic-constitutional, the topographic and the environmental) can be grasped only through these two media. Nevertheless, if we have not made structure and function the common denominator in the exposition of our paper but have resorted to a more conventional approach (environment, organism, fault in the organism) it is because we did not want to discuss the subject from the standpoint of pure logic, but rather practically, i.e., as it unfolds itself to the clinician. To him, structure and function appear as a scene made up of the environment, the organism, and the fault in the organism—the environment and the organism forming the distant and close background, the fault in the organism the focal point of his visual field. Structure and function as such, therefore, manifest themselves to the clinician primarily in the realm of pathology. Changes in the usual (healthy) structure and function are primary incentives for his activities. When these changes disappear, and are not expected to recur, his task is finished; the play he watched is over, or more precisely, the play within the play, for the play of the organism and the environment continues.

The metaphor just used, play within the play, clearly illustrates the common essential characteristic of the pathologic-morphologic and the pathologic-physiologic factors, and—with structure and function the keystone of the biologic sciences—also the keynote of the clinical entity itself. This keynote is the autonomous character of the flow of pathological dynamics, both structural and functional, in relation to the flow of life of the organism as such. As we have said, individual human life always takes an irreversibly finite course, regardless of sickness or health, but what we call the pathologic processes in this same organism may be reversible or irreversible, regressive or stationary or progressive (obviously the source for the old ontological concepts of disease). Basic concepts in general pathology (e.g., malignant tumor or fever) imply prognosis independent of that of the physiological course of life in multicellular organisms. It is important to recognize the two aspects of death—the physiological and the pathological.

In the present state of our knowledge, it is predominantly the pathologic-morphologic factor that reveals the course (pathogenesis through prognosis) of a clinical entity, for at present *general* pathologic anatomy is more highly developed than is *general* pathologic physiology. Pathologic-morphologic information, in addition to providing topographic knowledge, is of great significance for the clinician in characterizing the flow of disease. Morphologic changes *per se* are of significance only insofar as they actually or potentially influence systemic-organic function of a tissue or insofar as they result from disturbance of function.

It is the pathologic-physiologic factor in which the clinical entity and the process of diagnosing culminate, for it is some actual or anticipated limitation of his freedom of action which leads the patient to the physician, or which in

its potential (subclinical) form may be discovered by the physician incidentally (e.g., on the occasion of a draft or a life insurance examination). Organic and functional disturbances are often differentiated but both have, of course, a functional disturbance in common. The differentiation lies in the presence or absence of a structural basis for this functional disturbance. (At present the microscopic level of structure is generally taken as a basis —new technics might well alter this baseline.) However, what is the unit of functional disturbance or function in physiology comparable to the cell or the tissue or the organ as units of structure in morphology? The answer to this question reveals a significant cleavage that goes through the present-day human physiological investigation. Extensive specialization by the physiologist has advanced a multiplicity of functional units for consideration, all of value in delineating a clinical entity and in comprehending an individual patient, but with a wide scale of variation regarding the irreversibly finite flow of life. Systems have been fruitfully studied with a minimal amount of such consideration, while organs, tissues and cells, respectively, invite increasing attention to this viewpoint.

It is the aspect of unchanging ("scientific") dynamics that is predominant in studying the pathologic-physiologic factor today, and it seems hardly necessary to point out the extraordinary value of this attitude. The development of this aspect of dynamics has led and will continue to lead to great triumphs in the field of medicine; for as mentioned on page 488, the acceptance of "eternal laws" of nature is the primary basis for intervention and intervention is an ultimate task of the physician; but again—it is only an ultimate one. The physician has first to decide whether or not intervention is indicated. Identical physiologic disorders are not identical clinical entities. Obviously, the hyperthyroidism of acute thyroiditis must be differentiated from that of nodular goiter and the uremia of an acute glomerular nephritis from that of a contracted kidney. Knud Faber devotes the longest chapter of his book to functional diagnosis and says, "Functional diagnosis has directed the footsteps of the clinician who is interested in the methods and data of physiology back to the bedside, where his true kingdom lies . . ." (l.c., page 171). But he also writes, ". . . the functional disturbance is chiefly of interest to the clinician as a means to an end; he is interested in following the course and issue of disease . . ." (l.c., page 164). "Whenever its intimate connection with clinical observation has been broken medical science has been led astray again and again in the days of functional diagnosis as in the days of cellular pathology" (l.c., page 162).

It is not only the natural course, however, which may integrate the five factors mentioned so far, but also the therapeutically-induced one. The success of surgical intervention in restoring normal blood pressures in patients with renal lesions affecting only one kidney brought forth a "new" entity which had been previously entangled in essential hypertension, and for the practitioner, the success of sulfonamide therapy eliminated pneumococcus type differentiation in pneumonia.

To summarize, then, the previous discussion, the clinical entity is that concept in medicine that tries to delineate from the chaos of pathological phenomena multiple pictures in order to facilitate therapeutic research and practice. The depth and fullness of these pictures depend on the integration of scientific knowledge we have of the five factors discussed. Their vividness, however, is determined by the recognition of their flow, i.e., their courses. Trousseau says "to know the natural progress of diseases is more than the half of medicine." [13]

III

As already stated, this paper does not claim to contain anything new; its only aim is to bring to light some of a clinician's fundamental thought processes. Awareness of their essential character suggests four practical applications:

(1) *Patient Record.* A more systematic enumeration of the factors that compose the clinical entity should be attempted on the individual patient's chart. All five factors that play a rôle in diagnosing should be recorded, with degree of intensity when this is not indicated by the diagnostic term. Particularly, the tentative diagnosis should contain prognostic statements for the course under natural, as well as therapeutic, conditions. For example, simple peptic ulcer of the duodenum, mild, non-obstructive, early, slowly progressive, dietetically reversible; or, tabes dorsalis, severe, with widespread functional disturbance, late, moderately progressive, therapeutically irreversible.

(2) *Standard Nomenclature of Diseases.* This book could be a most inspiring stimulus for self-postgraduate education, but is instead the consternation of many physicians attending hospital patients. As we expressed it (1942) in a note, placed on the first page of the copies used at Hahnemann Hospital, San Francisco, California:

> The limitations of this book—its narrow basis, its rigidity, the rudimentary character of its pathodynamic viewpoints: e.g., its failure to work out the functional and psychic aspects, as well as to consider the intensity and reversibility of a disease—are obvious to every clinician. On the other hand, the book is the only attempt in recent medicine to develop a general concept of the disease entity. It thus furnishes, narrow as the underlying concept is, a unique occasion in which the clinician is compelled to organize his thoughts, particularly in unclear conditions. Therefore, in utilizing this book, the clinician provides himself with a continuous silent postgraduate education. To read pages VII, VIII, and IX will be of general interest to every physician.

A few simple symbols would suffice to add necessary information, individualize the history and not impair the practicability of the book. The following is suggested as a possible set of such symbols:

Psychologic Factors:

subclinical, incidentally discovered, unknown to both environment and patient

subclinical to patient, known to environment

subclinical to environment, known to patient

overt to both

Intensity:

mild

moderate

severe

Pathodynamic (Pathorrheic) Factors:*

early

intermediate

late

progressive

stationary

regressive

* RRHEIC from the Greek RHEO = I FLOW; cf. Dia-RRHEA, Pyo-RRHEA, etc. (Or River in the English language.)

(3) *The Clinical Pathological Conference.* There are several aims which a clinical pathological conference can pursue. One, for instance, is to educate the clinician to proper pathological classification on the basis of clinical data. This extolls the clinician who, with a minimum of data and regardless of how the data are collected, is able to provide the proper label of the case in question. It is the correct prediction of this label that counts, and it is immaterial, so far as the conference goes, whether the disease in question is reversible or irreversible, whether a misdiagnosis is made for an acute diffuse glomerular nephritis or for a polycystic kidney. Therapeutic implication is of secondary importance to this type of conference, and outstanding clinicians assert that to excell at the C.P.C. does not necessarily connote excellence at the bedside.

Another kind of C.P.C. might aim to emphasize therapy as the uppermost problem with classification only the means to this end. Under such conditions, the patient's history assumes an entirely different significance. Each observation recorded, large or small, each step taken, right or wrong, was related to the well-being of the patient, and had a meaning at that particular point. It would be necessary that the attending physician himself write that abstract. Only thus could the discussing physician at the conference clearly visualize the course of the disease as seen by the attending physician. Speculation would be confined as the basis of observation broadened. A most fruitful discussion would develop when the attending and the discussing physician disagreed. The final word would still rest with the pathologist, but in addition to his previous rôle, he would emphasize from his own viewpoint the answer to the burning question whether the lesions were reversible or irreversible. It would appear that the second type of clinical pathological conference might be of great significance in teaching. Richard Cabot himself, who introduced the C.P.C. as it is conducted today from the first viewpoint, may have had a similar thought in mind when he said in his *Differential Diagnosis*, ". . . diagnoses are missed—(a) usually because physical signs are not recognized; (b) occasionally because we do not think correctly." [3]

(4) *Training of the Family Physician.* The concept of the family physician is usually identified with that of the general practitioner. However, the two concepts are not identical. Actually the concept of the general practitioner embodies two different aims: (a) that of the family physician, and (b) that of the physician familiar with all the basic technical procedures in medicine. Today it has become questionable whether such integration can be maintained. It is becoming increasingly evident that a physician today can hardly keep abreast simultaneously with developments in the treatment of even the most frequent disorders seen in the various branches of medicine. The concept of the general practitioner from the technical point of view appears, therefore, to become a concept of the past. The other concept, which is associated with that of the general practitioner namely that of the family physician, is, on the other hand, not affected by the process of progressive specialization, and characterizes today and always, the basic concept of "the" physician; for as long as men will exist human beings will be individuals, in-dividuals throughout the course of their lives, wholes, but incomplete wholes, complete only with the inclusion of death (physiological death); and today as always it is the designated task of the family physician to take care of men as such in-dividuals, not at certain moments but throughout the course of their lives.

One possibility of training family physicians without obstructing the transformation of the general practitioner from the technical point of view into an ever increasing number of specialists would be to offer after the fourth year of undergraduate study combined rotating internships and assistant residencies in those branches of medicine that are united from the

point of view of the natural course of life: internal medicine (including infectious diseases and basic dermatology), psychiatry, pediatrics, and geriatrics. Fortunately, these branches are also still somewhat united from the aspect of their technics. Specialists agree that a competent family physician of such type could be trained in two years. It is true that he would not be able to perform emergency operations beyond highly qualified first aid. It would seem, however, that with such a family physician as basic health consultant all emergencies will be true emergencies and not emergencies arising because of the neglect of people to visit a physician in time. Rare as such true emergencies are, they are best taken care of by specialists and not by someone who may not have performed the required procedure for years even though he had once "learned" it.

Combined rotating internships and assistant residencies established in several medical schools and hospitals seem to indicate a trend in the outlined direction. (See Training of Physicians for Rural Practice by William J. Kerr in Second Annual California Rural Health Conference, October 16, 1948.)

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CASE REPORTS

SALMONELLA ENDOCARDITIS WITH STREPTOMYCIN FAILURE *

By Edward R. H. Kurz, M.D., F.A.C.P., Elmer L. Crehan, M.D., and Charles Thomson, M.D., *White River Junction, Vermont*

Many reports of endocardial infections, particularly of the subacute variety with response to intensive penicillin therapy, have recently appeared in the literature. Most of these cases are of the *Streptococcus viridans* type. Those associated with other organisms are infrequently reported. This is a report of a case of Salmonella endocarditis without a primary intestinal focus that failed to respond to penicillin, sulfadiazine, or streptomycin, although recognized in its incipiency.

The mortality rate in paratyphoid infections is so low that relatively few cases or necropsy reports can be found in the literature. Wells,[6] in reviewing the literature prior to 1904, discovered the mortality rate to be 3.5 per cent for *B. paratyphosus A*, and 4.2 per cent for *B. paratyphosus B*. He noted then that "of 320 necropsies in the paratyphoid infections endocarditis was observed in but one, nor was endocarditis observed in other single necropsies and smaller series, indicating that like typhoid, although a bacteremic disease, paratyphoid does not often lead to an infection of the heart valves."

The largest single series of cases was reported by Rathery and Ambard [4] in 1916. They observed 1,088 cases of paratyphosus B infections which were diagnosed either by positive blood cultures or agglutinations or both. They made no mention of any cases of endocarditis that were diagnosed clinically or observed post mortem.

Kretschmer [2] reported one case of paratyphoid B infection, without the usual intestinal lesions, which showed verrucous vegetations on the aortic cusps with miliary abscesses observed especially in the liver and spleen.

Meyer and Howell [3] reported a case of paratyphosus B infection with vegetations in the aortic and mitral valves which were superimposed on an old endocarditis which may have been rheumatic in nature.

Case Report

A 59 year old, white, single woodsman was admitted to this hospital for the second time September 12, 1946, with the chief complaint of chills and fever of six days' duration, and shortness of breath of one week's duration. The past history was entirely irrelevant. There was no antecedent history of typhoid or typhoid-like fever. There had been no previous gastrointestinal disturbance, and there was no history of rheumatic fever or rheumatism. The patient was first admitted to this hospital December 2, 1945, with the chief complaint of shortness of breath on exertion. The patient was discharged improved after one month's hospitalization, and the diagnosis

* Received for publication March 7, 1947.

at that time was coronary arteriosclerosis with auricular fibrillation. During the eight months prior to his final admission, the patient was able to get along fairly well on a sedentary routine. He still had slight dyspnea on exertion and on climbing stairs. There was no history of chest pain, ankle edema, or orthopnea. Six days prior to admission there was sudden onset of chills and fever. The chills were shaking in character; the exact height of the temperature was not known. The patient had three such attacks before entry. There were no other constitutional symptoms referable to acute infection. No other members of the family were ill at this time. It is noteworthy that the patient lived on a farm and that his water supply was derived from either springs or brooks in the vicinity. The patient also complained of an increase in dyspnea even on mild exertion during the seven days prior to admission. There was no chest pain. A slight productive cough had been noted but no frank hemoptysis or blood streaking.

Physical examination on admission revealed an obese, slightly cyanotic, elderly, white male in moderate respiratory distress. Temperature 98°, pulse 104, respiration 24, blood pressure 100 mm. of mercury systolic and 66 mm. diastolic. The left pupil did not react to light, and ophthalmoscopic examination revealed moderate pallor of the left optic disk. There was no engorgement of the cervical veins. The chest expansions were diminished bilaterally but were equal. There was slight dullness and many moist, crepitant râles at the right base, posteriorly. There were a few moist râles at the left base, posteriorly. There was moderate cardiac enlargement and the rhythm was totally irregular. A loud systolic murmur was heard over the entire precordium; it was harsh and maximal in the aortic area and was transmitted to the neck vessels. A_2 was absent. There were no thrills and there was no diastolic murmur. The liver seemed to be moderately enlarged, although its edge could not be felt. There was no clubbing of the fingers. No petechiae were seen in the skin, conjunctivae, nailbeds, or mucous membranes of the mouth.

Laboratory Data: On admission, red blood count was 4,240,000, with 13 grams hemoglobin, white blood count 5,400 with polynuclears 78, lymphocytes 17 and monocytes 5 per cent. Blood serologic test for syphilis was negative; urine showed two plus albumin. Sedimentation rate was 93. Blood cultures, taken on September 26 and 30, October 30, November 8, 9, 12, and 13, revealed pure cultures of a gram negative organism which had the cultural characteristics and sugar fermentation reactions of paratyphosus B. Further bacteriological studies performed in the Bacteriology Department of the Yale University School of Medicine revealed the organism to be *Salmonella minnesota*. Agglutinations performed with paratyphosus B antiserum on September 26 and 30 were positive in dilutions of 1–320 and 1–2560, respectively. Bacterial colony counts performed November 8, 9, 12, and 13, were 3 per c.c., 4 per c.c., 1 per c.c. and 2 per c.c., respectively. Non-protein nitrogen determinations on November 4 were 66 mm. per 100 c.c., and on November 12, 84 mm. per 100 c.c. Sulfadiazine level on November 14 was 15 mm. per c.c. All subsequent urinalyses showed a one to two plus albumin with occasional white blood cell per high power field. There were no red blood cells in the urine. The white blood cells ranged between 5,400 and 12,700 and the polynuclears ranged between 70 and 90. The organisms obtained from the blood were tested and found to be slightly sensitive to streptomycin. Seven stool cultures and two urine cultures were negative for pathogenic organisms. On November 30 the red blood count was 3,340,000, with 12.8 grams hemoglobin.

Clinical Course: Patient was afebrile for the first five hospital days. The electrocardiogram on admission showed absent P-waves and an absent R-wave in Lead IV. Fluoroscopic and roentgen-ray examination of the chest, taken December 3, 1945, revealed the trachea to be slightly deviated to the right; the diaphragms were high, and there was both right and left ventricular enlargement (figures 1 and 2). On

September 18, the patient's temperature rose to 102° and he had an accompanying severe, shaking chill. Chest roentgen-ray and physical examination were essentially the same as on entry. Patient was then given 200,000 units of penicillin daily for six days without relief, so the therapy was discontinued. Patient was uncoöperative and antagonistic and at times appeared to be slightly irrational. He continued to have a daily rise in temperature to 100° or 101°, and on October 1 streptomycin therapy was instituted. Six grams of streptomycin were given daily for three days without

FIG. 1. December 3, 1945.

response. Because of the lack of therapeutic effect and because of the inaccessibility of the drug, this therapy had to be discontinued. From October 4 to 31, no specific antibiotic therapy was used. The patient's clinical course gradually declined. On October 31, patient again started to have a daily rise in temperature to 102° and 103°, so sulfadiazine therapy was started. He was given eight grams daily, by the oral method, along with equal doses of sodium bicarbonate. On November 3, patient

suddenly became dyspneic, hyperpneic, and cyanotic. He experienced a shaking chill which was followed by a rise in temperature to 104°. Physical examination at this time revealed numerous, moist râles over both lung fields posteriorly, and petechiae in both conjunctivae. The spleen was not palpable but appeared to be enlarged to percussion. The liver was four fingers below the right costal margin and slightly

FIG. 2. November 7, 1946.

tender. A portable chest film revealed the diaphragms to be high, and there was a considerable mottled, hazy reaction throughout both lung fields with several areas of confluent consolidation, suggesting the possibility of pulmonary infarctions with superimposed congestive changes. The patient was put in an oxygen tent and appeared to improve. The sulfadiazine therapy was continued until November 7, then was stopped

because patient still had a daily temperature rise to 103° or 104°. On November 9, streptomycin was obtained and this therapy was again instituted. Patient was given six grams daily. The same day patient complained of right upper quadrant abdominal pain. The liver was four fingers below the right costal margin and tender. There seemed to be some tenderness and spasm in the left upper quadrant but the spleen was still not palpable. On November 10, the patient again had a shower of petechiae in the conjunctivae with a temperature rise to 104.8°. His condition became progressively worse and patient died on November 14, after six days of streptomycin therapy.

Pathological Discussion

At post mortem, the body was that of a well-developed and nourished white male, measuring 170 cm. in length and having an estimated weight of 150 pounds. There were petechial hemorrhages in each conjunctiva. There was moderate cyanosis of the nailbeds. No edema was detected.

Fig. 3.

Incision revealed a panniculus adiposus of 0.7 cm. with 10 c.c. of clear, yellow, serous fluid in the peritoneal cavity. The greater omentum was plastered to the spleen by firm adhesions. When these were broken an estimated 300 c.c. of purulent liquid was expressed from a splenic abscess. The left pleural cavity contained 200 c.c. of clear, yellow fluid and the right 100 c.c. There were no adhesions.

The pericardial sac contained 100 c.c. of cloudy, yellow fluid. The heart weighed 775 grams. There were prominent, small, dilated vessels and petechiae most prominent over the left auricle. On the left auricular wall, just above the mitral valve, there was a 2 cm. gray, darkened area to which was attached a red, shaggy, friable vegetation. There was some thickening of the mitral valve, but no changes suggestive of old rheumatic valvulitis. The aortic valve was partially replaced by

massive, friable, red-brown vegetations most marked over the anterior portion of the valve (figure 3). The septum between the right and posterior cusps was absent. The valve was calcified and cut with difficulty. The left coronary artery, proximal to its bifurcation, was dilated to a diameter of 1 cm. for a distance of 1 cm. Section surface of the myocardium revealed numerous, gray-white areas, ranging from 0.5 to 1 cm. in diameter. Microscopically there were collections of lymphocytes and plasma cells, with a few scattered polymorphonuclear leukocytes between muscle fibers. There were no collections of cells suggestive of Aschoff bodies. In many areas cardiac muscle was replaced by fibrous tissue. Cultures and smears of the vegetations on the heart valves also demonstrated a pure culture of *Salmonella minnesota*.

The right lung weighed 660 grams, and the left 700 grams. Both lower lobes exhibited increased resistance and decreased crepitance, and the surface made by cutting exuded gray-pink, frothy fluid. Microscopically many of the alveoli were dilated and filled with amorphous pink staining material. In areas surrounding smaller bronchi, some alveoli were collapsed. Collections of lymphocytes, plasma cells and large macrophages containing light brown material were found both in the alveoli and in the interstitial tissue.

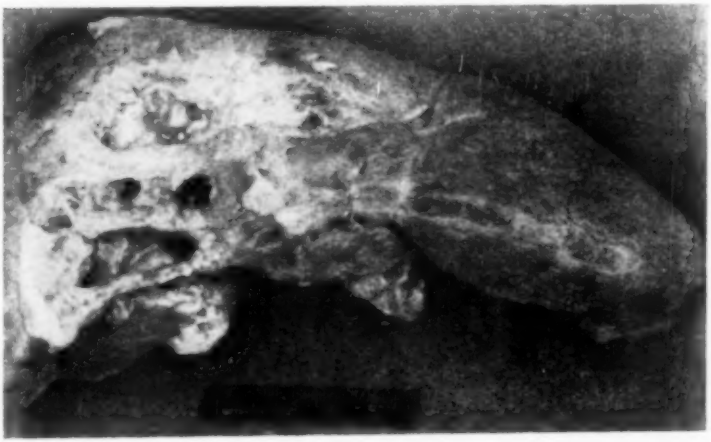

FIG. 4

The liver weighed 2,750 grams and was grossly and microscopically normal. The gall-bladder contained 15 c.c. of green-black, mucoid fluid and a single green-black mixed pigment cholesterol calculus 1 cm. in diameter. The wall was thickened and scarred. Material from the gall-bladder yielded a pure culture of *Salmonella minnesota*.

The spleen weighed 575 grams and was soft. On the anterior superior margin there was a 5 cm. defect from which exuded foul, yellow-brown material. The abscess wall was yellow-brown and soft (figure 4). Microscopically a section through the abscess showed necrotic debris surrounded by a thin, fibrous wall. The remaining spleen was microscopically normal. The gastrointestinal tract was normal.

The kidneys weighed 260 grams each. On the external surfaces there were

several dark red, depressed areas as a result of old infarcts. Microscopically both kidneys showed many collections of lymphocytes and a few polymorphonuclear leukocytes in the interstitial tissues of pyramids and the cortices. Many of the tubules contained casts and cellular debris. The remainder of the urogenital system was grossly and microscopically normal.

The central nervous system was normal, both grossly and microscopically.

Anatomic Diagnoses: 1. *Salmonella minnesota* endocarditis, aortic and mitral valves, left ventricle and left auricle. 2. Calcareous aortic stenosis. 3. Chronic myocarditis. 4. Abscess of spleen. 5. Chronic pyelonephritis (bilateral). 6. Hypertrophy of the heart (775/375). 7. Focal fibrosis of myocardium. 8. Hydrothorax, 200 c.c. left; 100 c.c. right. 9. Old infarcts of kidneys. 10. Chronic cholecystitis. 11. Cholelithiasis (one stone).

Comment

The etiological organism in this case, recovered by numerous cultures from the blood stream, proved to be *Salmonella minnesota*. At post mortem an intensive search for a primary focus, other than the heart valves, for the source of this organism was made. Gross examination of the gastrointestional tract revealed no abnormalities. The gall-bladder, other than for a calculus, appeared normal. However, from the gall-bladder proper at post mortem the same organism that was cultured in life was obtained. Whether this was the primary focus or a concomitant infection, we are unable to state.

Discussion as to the underlying pathological cause of the stenosis revealed no history or microscopic changes on the aortic or mitral valves that would lead one to believe that it was due to an underlying rheumatic infection.

This case was treated with all three known antibiotics and, although the diagnosis was made early clinically, the patient's course declined rapidly with ultimate death.

Summary

Herewith is presented a case of *Salmonella minnesota* infection of the aortic valve, superimposed on an aortic stenosis with bacteremia and septic infection of the spleen, resulting in death despite the use of antibiotics, especially streptomycin.

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THE ELECTROCARDIOGRAPHIC SYNDROME FOLLOWING PAROXYSMAL TACHYCARDIA *

By JOHN G. SMITH, M.D., *Rocky Mount, North Carolina*

SEVERE and prolonged abnormalities of the limb and chest leads in the electrocardiogram may follow paroxysmal ventricular tachycardia, and have led to serious errors in diagnosis. This report deals with the occurrence of an electrocardiographic syndrome following an attack of paroxysmal tachycardia, apparently ventricular in origin, developing in a healthy young male without demonstrable evidence of organic heart disease. The literature has been recently and ably reviewed by Smith,[1] who cited 26 cases of this electrocardiographic syndrome accumulated since early interest was aroused by Burak and Scherf,[2] and Graybiel and White.[3] It is the purpose of this report further to emphasize the not infrequent occurrence of paroxysmal ventricular tachycardia without preceding or subsequent damage to the heart [4, 5, 6, 7] and to report a case demonstrating the electrocardiographic syndrome that may follow paroxysmal ventricular tachycardia.

The importance of this abnormality, alarming only to those unfamiliar with it, lies in its confusion with ECG signs generally recognized as indicating severe damage to the heart, and its occasional occurrence in hearts that are normal. In Smith's [1] review only three of the 26 cited cases were thought to have clinical heart disease, and two autopsied cases did not have demonstrable heart disease.

The case here reported has, upon repeated physical and laboratory examinations, failed to show any evidence of cardiac or other disease, and is a manual laborer having an excellent exercise tolerance. No adequate explanations have been offered for the occasional occurrence of this synchrome and for its absence in the majority of lengthy attacks of paroxysmal tachycardia.

CASE REPORT

A 29 year old white married male of robust physique was first seen on November 8, 1946, complaining of "palpitation."

The past medical history was non-informative with the exception of a rather benign attack of pneumonia at the age of 14 years. During the previous seven years the patient had episodes of rapid heart action on an average of two to three times yearly, varying from one a month to one a year, with no tendency toward increase in the frequency of occurrence or severity and duration of the episodes, the latter being usually about six hours. These seizures began suddenly, usually during the wakeful and active hours of the day, and were characterized by a violent, tumultuous and "fluttering" sensation in the precordial area deep within the chest, associated early in their course with exhausting and profound weakness such that the patient had developed the habit of going to bed immediately an episode developed. During one of the earlier attacks the patient became unconscious for about an hour with spontaneous recovery without sequelae. The seizures had generally subsided abruptly of their own spontaneity, leaving the patient rather weakened for the ensuing one or two days. During the interval between these episodes the patient had enjoyed excellent health, being engaged actively as a field electrician with a splendid exercise tolerance and no symptoms of a cardiorespiratory nature.

* Received for publication February 24, 1948.
From Boice-Willis Clinic, Park View Hospital.

During the initial examination November 8, 1946, the patient was acutely restless although in no obvious respiratory embarrassment, somewhat pale with beads of perspiration on the upper lip and covering the brow. General examination was negative with the exception of a pulse rate approximately 180 per minute. The first electrocardiogram, made about seven hours after the episode began (figure 1), showed paroxysmal tachycardia with a QRS interval of 0.14 second, and a ventricular rate absolutely constant at 188 per minute. Following the examination, the patient in-

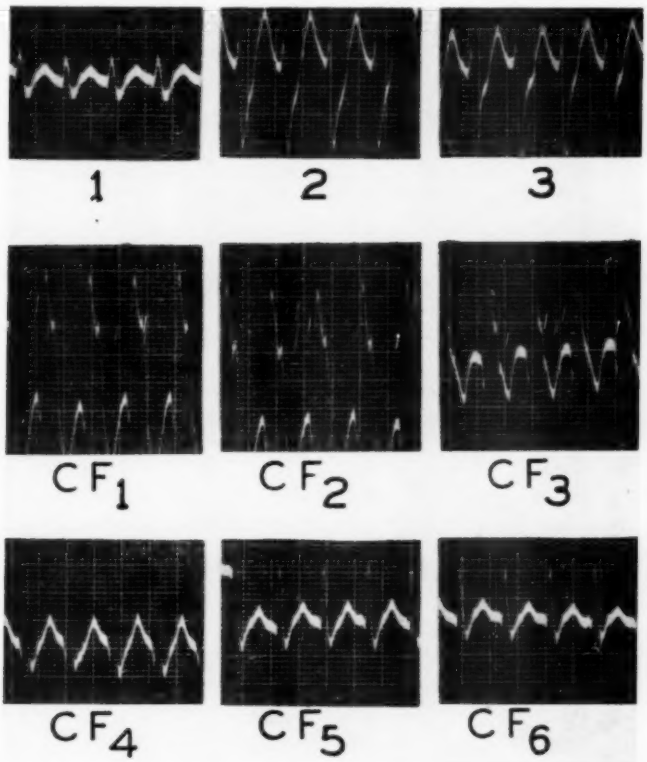

FIG. 1. C.V.B., November 8, 1946. Electrocardiogram made seven hours after onset of the tachycardia, presumably ventricular in origin.

sisted upon driving his car home, a distance of some 17 miles, where he continued under the observation of his referring physician, who, on the following afternoon, gave the patient 3 grains of quinidine sulfate every four to six hours by mouth. After the second dose the attack subsided, having lasted a total of 26 hours.

Three days following the onset of this episode (or two days after its subsidence) the patient returned for his second electrocardiogram. At this time he had been at least 40 hours without medication, had completely recovered his composure and sense

of well-being and was entirely asymptomatic. An electrocardiogram (figure 2, November 11, 1946) showed a reversion to normal sinus rhythm with a QRS interval of 0.09 second and a P–R interval of 0.22 second. The heart rate was 72 per minute. This electrocardiogram showed a striking depression of the RS–T segments and in-

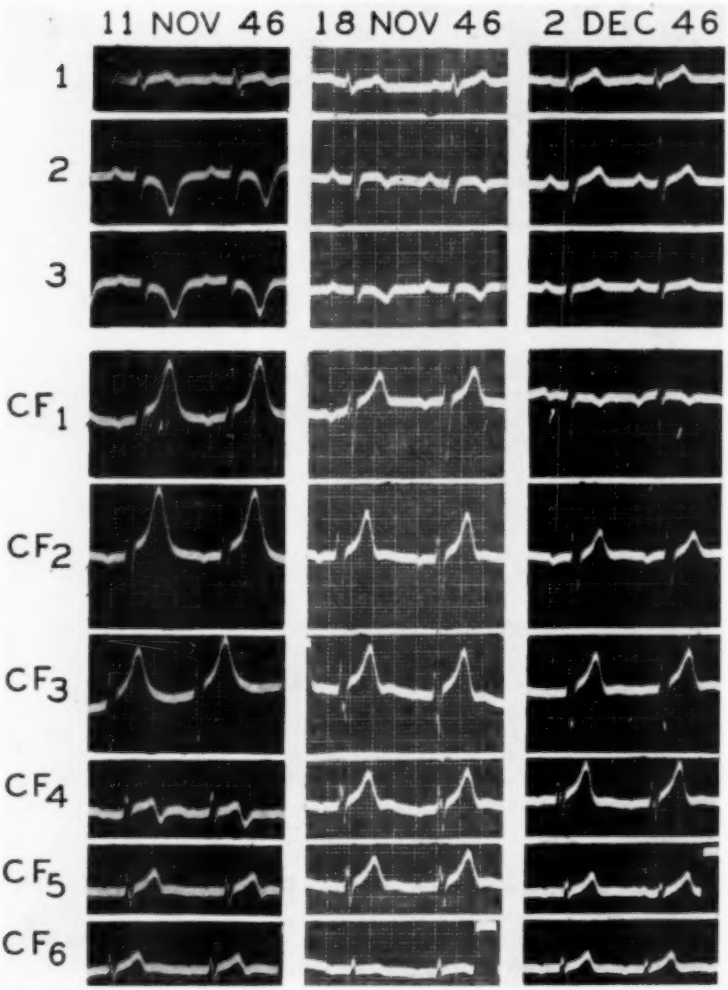

FIG. 2. The ECG dated November 11, 1946 was made two days after abrupt offset of an attack of paroxysmal tachycardia lasting 26 hours, and it demonstrates the severity of this post-tachycardia electrocardiographic syndrome. The ECG dated November 18, 1946 was taken nine days, and the one dated December 2, 1946, 23 days after subsidence of the attack.

version of the T waves in Leads II and III with a widening of the Q–T interval to 0.48 second. Deep S waves were persistent throughout all limb leads and there was a late T_1 inversion. The chest leads showed conspicuously tall T waves in $CF_{1, 2 \text{ and } 3}$ with late inversion of the T waves in $CF_{4, 5 \text{ and } 6}$. A physical examination at this time was again completely negative, blood pressure 120/80, white blood count 14,200; polymorphonuclears 72 per cent; red blood count 4.52; hemoglobin 88 per cent, blood Mazzini test negative, and sedimentation rate normal. Chest fluoroscopy was normal, the heart and great vessel shadows being well within normal limits. Subsequent electrocardiograms (figure 2) made nine days (November 18, 1946) and 23 days (December 2, 1946) after subsidence of the attack showed persistency of the P–R interval at 0.22 second and QRS interval at 0.09 second, lessening of the T wave inversion in the limb leads, changing to upright T waves in all limb leads on the twenty-third day following cessation of the attack. The RS–T segment alterations had disappeared by the ninth day. Physical examinations on each of the days in which electrocardiograms were done were negative, and sedimentation rates in each instance were normal.

Discussion

Close analysis of the initial cardiogram (figure 1, November 8, 1946) made at the seventh hour of the episode of rapid heart action showed QRS–T complexes of the same character within each lead, suggesting unifocal origin of the ectopic beats. The actual effect of the rapid heart action on the sinus node cannot be determined in this instance since it is impossible to make out the P waves during the paroxysm, and no record is available of the onset of the episode; in the absence of recognizable P waves, it is possible but improbable that this may represent an instance of supraventricular paroxysmal tachycardia with intraventricular block, but this is unlikely because the intraventricular block had disappeared in the first tracing following cessation of the ectopic rhythm, suggesting that the intraventricular block was related to the rapid heart beating rather than a preexistent bundle branch block; furthermore, there is no similarity of contour of the QRS configuration in the tracing made during and after the abnormal rhythm. Katz [8] has recently published records demonstrating the value of the QRS pattern occurring between attacks of paroxysmal tachycardia in distinguishing between one of a supraventricular origin associated with intraventricular block, and one of pure ventricular origin. Supporting the belief that this tachycardia was ventricular in origin is the fact that carotid sinus massage had no effect on the rate or rhythm.

The ECG abnormalities of the cardiogram (figure 2, November 11, 1946) made two days after cessation of the 24 hour attack of rapid heart action showed depression of $RS–T_{2 \text{ and } 3}$ with plus-minus diphasicity of T_1, a striking inversion of $T_{2 \text{ and } 3}$ having broad bases with equal limbs, and prolongation of Q–T interval (actual 0.48 second, as compared to predicted upper limit of normal at 0.40 second, using the Ashman-Hull [9] formulae). In addition, important changes occurred in the chest leads: there was elevation of RS–T segments in $CF_{1, 2 \text{ and } 3}$ with conspicuously tall and upright T waves, having very broad bases and almost equal limbs; in CF_4 there was definite late inversion of the T wave—resembling somewhat that of Lead I—and late T wave inversion in the $CF_{5 \text{ and } 6}$ positions. The subsequent cardiograms showed a gradual restoration to normal, with recovery of the RS–T segment deviation in limb and chest leads by the ninth day after cessation of the attack (figure 2, November 18, 1946), and recovery of T

wave changes not complete until the cardiogram made 133 days later (figure 4, March 29, 1947). It is noteworthy that T waves of $CF_{1, and\ 2}$, having their expected inversion in the normal adult cardiogram, were so sharply deformed following the acute paroxysm. Figure 4 shows a final tracing (July 5, 1947) which was made approximately three months after the first recovery pattern

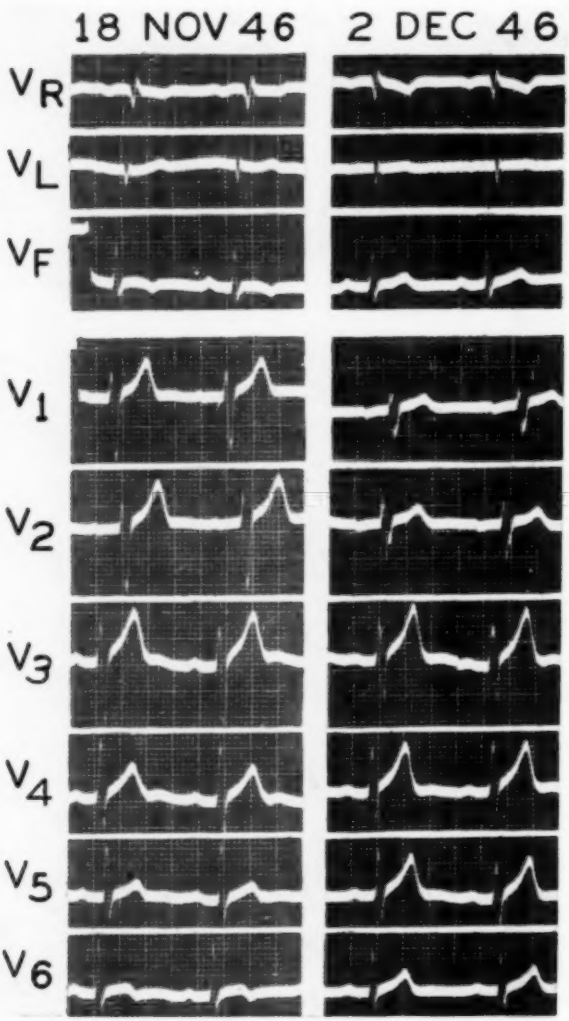

FIG. 3. Unipolar leads (Wilson type) made on the ninth and twenty-third days after abrupt offset of the paroxysm of tachycardia.

(March 29, 1947) in order to demonstrate its stability at normal values. In all the electrocardiograms following the initial episode of tachycardia, there is a P–R interval varying from 0.22 to 0.24 second in accordance with the heart rate and representing what is apparently "normal" for this heart. Recent studies of

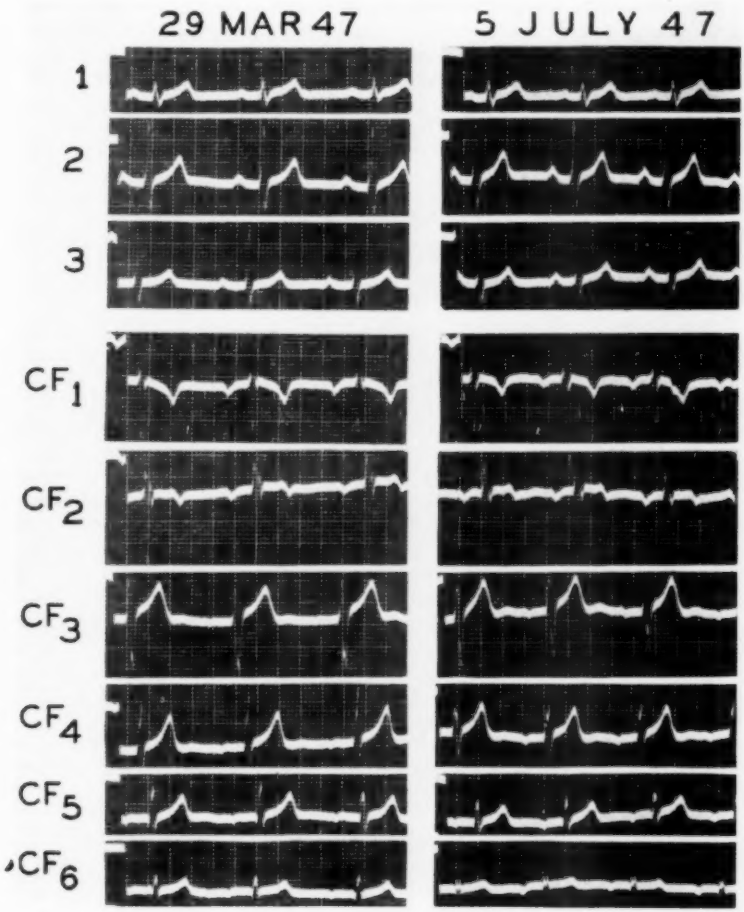

FIG. 4. The electrocardiogram dated March 29, 1947 was made 123 days after offset of the tachycardia; the tracing dated July 5, 1947 shows stabilization of the two records at normal values except for prolongation of P–R intervals.

Graybiel et al.[10] reported P–R intervals of 0.22 second or greater in 12 out of 1000 healthy aviators; Hall, Stewart, and Manning[11] found P–R intervals greater than 0.20 second in nearly 2 per cent of 2000 RCAF aircrew.

Figure 3 represents unipolar (Wilson type) limb and chest leads made in addition to the standard limb and $CF_{1, to 6}$ chest leads.

These changes in the S–T segments, the T waves, and duration of Q–T intervals constitute an established pattern which may follow paroxysmal ventricular tachycardia, but which is not necessarily peculiar to this state. The pattern in this case conforms to the T_3 type deformity of Cossio, Vedoya, and Berconsky [12] and of Smith,[1] in which left axis deviation during the paroxysmal ventricular tachycardia was associated in the post-tachycardia ECG with negative T_3 or negative $T_{2 and 3}$ waves. When these changes were present in Lead I or Leads I and II, it was designed as the T_1 type, although negative T waves in all three limb leads were noted at times. The peculiar disturbance of this post-tachycardial ECG was not brought about by medications, for the patient received only quinidine sulfate, a total of 21 grains, the last dose being taken 40 hours prior to the first post-tachycardial electrocardiogram, dated November 11, 1946. It has been established that the action of orally administered quinidine on the heart generally reaches a maximum in two to four hours,[13, 14] and largely subsides in 24 hours.

SUMMARY

1. The post-tachycardia ECG syndrome is of importance primarily in its possible confusion with ECG changes denoting a more serious disorder; once recognized, the syndrome is easily identified by serial ECG.

2. A case is reported of a patient having no demonstrable signs of structural heart disease but whose electrocardiograms showed this syndrome following paroxysmal tachycardia.

3. Usual characteristics of the syndrome are depression of S–T segments occurring in limb leads having T waves markedly inverted with broad bases and almost equal limbs; prolongation of Q–T intervals; alteration of S–T segments and marked changes in height and direction of T waves in chest leads; gradual regression to normal over a variable period of many days.

4. This syndrome occurs generally in young patients without organic heart disease and is especially frequent following tachycardia of ventricular origin.

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STREPTOMYCIN THERAPY OF *HEMOPHILUS INFLUENZAE* ENDOCARDITIS LENTA *

By William S. Middleton, M.D., F.A.C.P., *Madison, Wisconsin*

Renewed interest in the etiology of endocarditis lenta has been a natural by-product of the availability of a series of agents with therapeutic promise. The success attendant upon the use of penicillin in treating *Streptococcus viridans* endocarditis lenta gave further impetus to similar attacks upon other etiologic backgrounds. Among these, *Hemophilus influenzae* and *para-influenzae* invited particular attention by reason of their sensitivity to streptomycin.

The incidence of *Hemophilus influenzae* and *para-influenzae* endocarditis is probably less common than Thayer's 2.94 per cent.[1] In 1940 Craven, Poston and Orgain [2] collected only 36 instances of this condition from the literature, to which they added two patients. Rose,[3] Hunter and Duane [4] and Martin and Spink [5] likewise emphasized its rarity. By reason of this circumstance and the remarkable clinical response to streptomycin this case record is posted:

A 37 year old white farmer was admitted to the Wisconsin General Hospital, September 30, 1946, complaining of chills and fever.

In the spring of 1945 the patient had noticed the gradual onset of malaise and easy fatigue. In about six weeks chills made their appearance. The first chill lasted about one-half hour and was succeeded by fever of 103° Fahrenheit for three hours. The interval between the chills decreased until they were occurring about a week apart. On two occasions there were two chills at two hour intervals in the same day. The chills lasted from 20 to 35 minutes and the fever, usually for about three hours. The sweating was profuse. Frequently after the fever there were observed local areas of discoloration 2.5 to 3 cm. in diameter with spontaneous aching and marked tenderness. These remained painful for about a week to 10 days.

The patient came under the care of several physicians beginning July 22, 1945.

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From the Department of Medicine, University of Wisconsin Medical School.

At their hands he was repeatedly treated with penicillin with apparent transient benefit. On two occasions (June 1, 1946 and July 1, 1946) in different laboratories an unidentified small gram negative bacillus had been isolated from blood cultures. In neither instance was cognizance taken of this finding. The patient states that the areas of described discoloration and tenderness appeared recurrently on the outer aspect of the thigh, soles of the feet, shoulders and lower arms over the intervening period. Muscular movement became intensely painful at times. The latest area of local discomfort in the palm of the right hand, attended a chill. At present there is some tenderness about the umbilicus which according to his statement followed a chill and fever two days before admittance. The patient has lost 11 pounds in the last year.

The inventory by systems added only recurrent sore throats and nocturia. Rheumatic fever had confined the patient to bed for seven weeks when he was 16 years old. Two quarts of pasteurized milk were consumed daily in 1945. The social and family histories were irrelevant.

Upon physical examination unusual pallor and some wasting were noted. There was a capillary pulse in the lips. The radial pulse had a dicrotic quality. The finger nails showed a watch-crystal configuration. The apical impulse was diffuse and displaced to the left. There was a double thrill at the apex. The left border of the heart was 14.5 cm. from the midsternal line in the sixth interspace. A low-pitched presystolic murmur led up to the mitral first sound. There was a loud, low-pitched, blowing systolic murmur partially replacing the first sound at the apex, transmitted well into the axilla. The blood pressure was 118 mm. Hg systolic and 68 mm. diastolic. Marked tenderness was noted in an area 5 cm. long and 2.5 cm. wide about the umbilicus. The liver was 2 cm. below the right costal margin and slightly tender. The spleen and the right kidney were palpable.

The laboratory examinations were significant only in the absent agglutinations for brucella, *B. tularense*, and *E. typhosa*, microscopic hematuria and the blood cultures repeatedly positive for a gram negative bacillus. This microörganism was eventually identified as *Hemophilus influenzae*. One disquieting factor entered into the differential considerations in the positive opsonocytophagic index for brucella.

Before there was a clear definition of the etiology, streptomycin was begun in 0.5 gm. doses every six hours. This dosage was continued after the isolation and identification of *Hemophilus influenzae* for a total of 24 days. The temperature, which had been running an intermittent course from 99.6° to 102°, fell sharply to normal in 48 hours and only once went above 99° during the remainder of the hospital stay.

The *Hemophilus influenzae* was inhibited by 0.6 microgram of streptomycin per c.c. (in vitro), while levels of as high as 20 micrograms per c.c. of serum were attained on the ninth day of therapy. Incidentally, 10 units of penicillin were required for bacteriostasis. Dizziness and vertigo were remarked on the eighteenth day of streptomycin. The blood cultures became negative for *Hemophilus influenzae* on all cultures subsequent to the institution of streptomycin therapy and the patient, repeatedly seen in the intervening year, has been free from evidence of relapsing symptoms and signs at all times. Signs of aortic insufficiency have supervened but compensation has been adequate under the physical limitations imposed. The last recheck on September 3 to September 5, 1947, confirmed the control of the infectious process in the normal temperature, stable clinical status, and negative blood cultures. There remained only the minimal vestibular hypofunction to caloric tests.

The prompt and sustained effect of streptomycin in controlling the *Hemophilus influenzae* infection in this patient is noteworthy. Priest and McGee [6] suggested the availability of streptomycin in *Hemophilus influenzae* and *para-influenzae* infections on the basis of the in vitro sensitivity; but their patient with the latter etiology had been cured by penicillin and sulfamerazine. Hunter and

Duane [4] and Bland and Peterson [7] have reported isolated instances of the clinical cure of *Hemophilus influenzae* or *para-influenzae* endocarditis lenta by streptomycin. (The latter authors indicate a second arrest of this infection under streptomycin.) Although this condition may be unusual, its earlier diagnosis in the patient herein discussed was twice overlooked by competent clinical pathologists and clinicians through the neglect of positive returns upon blood culture. Possibly this etiology of endocarditis lenta may not be as rare as is generally assumed.

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VENA CAVAL THROMBOSIS WITH POLYCYTHEMIA AND LEG ULCER*

By John A. Boone, M.D., F.A.C.P., and Horace G. Smithy, M.D.,†
Charleston, South Carolina

The first case of vena caval thrombosis associated with polycythemia was reported by Ragins and Coe in 1943.[1] In their patient the polycythemia developed under observation subsequent to a thrombosis of both the superior and inferior vena cava. The patient did not recover and an autopsy disclosed the vena caval obstruction which had been suspected clinically. Before the thrombosis the hemoglobin was 85 per cent and the red blood count 4,900,000. After the thrombosis the hemoglobin rose to 100 per cent and the red blood count to 7,960,000.

We wish to report a similar case which recovered and subsequently developed varicose ulcers of the legs.

Case Report

The patient, a white female aged 61 years, entered Roper Hospital on February 2, 1946, complaining of pain in the legs. Two years previously she had awakened one morning "swollen all over," and the joints of her entire body became stiff. Her local

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† Deceased.

rural physician told her she had mumps. She was extremely weak, and was unable to get out of bed for six months. During this period the generalized swelling gradually subsided. When she was able to walk she noticed a purplish discoloration of both legs which has persisted. Since then she has been troubled by dizziness, loss of memory and mental confusion, and by blurring of vision. One year after the original episode, she bruised the right shin and an ulcer developed at the site of injury. This had alternately healed and recurred since then. She was referred to one of us for treatment of pain in the affected leg in February, 1946.

FIG. 1.

Examination disclosed a well-nourished elderly woman whose skin was of a reddish-cyanotic tint. The conjunctivae were engorged, the lips cyanotic and the tongue of a deep red, beefy appearance. Over most of the trunk were noted dilated, tortuous veins, particularly over the abdomen and flanks, which were continuous with similar veins over the thighs and legs. The lungs were clear. The heart was moderately enlarged, its rate slow and regular, and there were no murmurs. Blood pressure was 180 mm. Hg systolic; 90 diastolic. The abdomen was obese but showed no shifting dullness. Liver and spleen were palpable on deep inspiration. Both legs

showed pronounced dependent cyanosis and rubor and numerous small superficial varices. In the right leg there was a questionably positive Homans' sign, deep calf tenderness and acute tenderness in the femoral triangle. There was no edema, but the patient had been in bed several weeks. Both posterior tibial pulses were palpable; both anterior tibial pulses were absent. There was a healed ulceration on the lower third of the right leg with surrounding pigmentation.

Laboratory studies showed the urine within normal limits. The red blood count was 7,650,000, the hemoglobin 18 grams per 100 c.c., the white blood count 13,700 with 81 per cent polymorphonuclears.

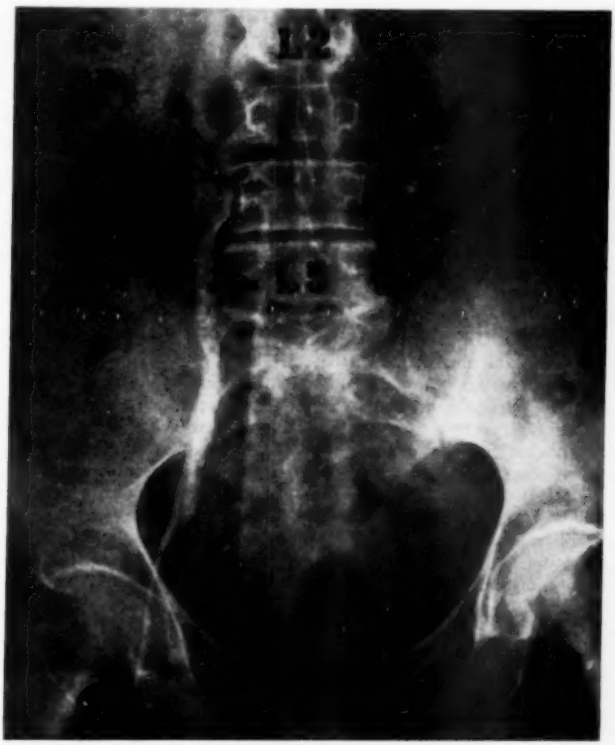

FIG. 2.

It was thought that the patient had an acute recurrent thrombophlebitis in the right leg. A novocaine block of the right lumbar sympathetic chain resulted in complete elimination of pain, Homans' sign and palpatory tenderness. Her general condition was not considered sufficiently good to permit the performance of lumbar sympathectomy. Accordingly, an alcohol injection of the right lumbar sympathetic chain was done and the patient was discharged. She remained free of pain for several months. In June, 1946, she developed upper abdominal pain, nausea and vomit-

ing, and jaundice. She entered a hospital in another city, where the gall-bladder was removed and found to contain stones. The operative note states: "There were varicosities in the abdominal wall and in the omentum."

In December, 1946, the patient consulted us again for a recent recurrence of the leg ulcer and pain. On this admission the physical findings were similar to those previously. The red blood count was 9,020,000, the hemoglobin 18.5 gm. per 100 c.c. The leg ulcer improved under the therapy of hot wet dressings and penicillin. A phlebotomy of 500 c.c. resulted in reduction of the red blood count to 7,730,000 and the hemoglobin to 18.0 gm. A photograph on infra-red film (figure 1) shows the varicosities demonstrable on this occasion. She was discharged to return for further treatment.

She was again seen in January, 1947, when the red blood count was 7,770,000 and the hemoglobin 20 gm. Three phlebotomies of 500 c.c. each brought the red blood count to 5,300,000 and the hemoglobin to 16.5 gm. per 100 c.c. In an effort to reduce venous stasis in the ulcerated extremity, the saphenous venous system was sclerosed by the combined ligation-injection technic.[2] At the same time venograms of the vena cava were made for the purpose of demonstrating suspected vena caval obstruction. The right sapheno-femoral junction was exposed under local infiltration anesthesia by a short transverse incision over the fossa ovalis of the thigh. After high division of the main saphenous trunk, its distal segment was injected segmentally with 5 c.c. of an aqueous solution of sodium morrhuate in the usual manner through a ureteral catheter.[2] The proximal stump of the divided saphenous vein then was catheterized, a No. 5 ureteral catheter being passed cephalad into the iliac vein. Serial radiographs were made in rapid succession during the subsequent injection of 60 c.c. of Diodrast through the catheter. Figure 2 shows arrest of the dye within the vena cava at the level of the fourth lumbar vertebra. This was interpreted by the radiologist as representing an obstruction of the vena cava.

During the first four postoperative days the patient complained of persistent pain at the site of the ulcer despite the fact that the latter showed considerable improvement. On the fifth post-operative day, a right lumbar sympathetic nerve block was done with procaine, followed immediately by the injection of alcohol (95 per cent) at the level of the second and third lumbar segments, 1 c.c. being injected at each level. This resulted in considerable decrease, but not complete disappearance, of pain in the ulcer. Meanwhile, there was noted a marked improvement in the patient's general condition as a result of the phlebotomies. She became alert and cheerful and lost the sensation of "fullness in the head." Her mental confusion disappeared and vertigo was no longer noted. She was discharged on the seventh post-operative day in good condition.

Since then she has been examined at intervals by her local physician, who has done phlebotomies of approximately 500 c.c. as often as necessary to keep the red blood count within normal limits. He reports that she is still having trouble with the leg ulcer, but that she has been mentally clear and finds her eyesight much better since the phlebotomies were begun.

Discussion

It is, of course, impossible to be certain whether in this case the vena caval thrombosis preceded the polycythemia or vice versa, though the former possibility is suggested by her apparent perfect health before the thrombosis. The fact that she "swelled up all over" and a physician thought of mumps suggests that the superior vena cava was involved as well as the inferior (figure 1).

It is hoped that in future reports of cases of vena caval thrombosis more attention will be paid to the red blood cell counts, for it may be that important light will be shed on the mechanism of polycythemia vera.

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PERSISTENT TACHYCARDIA CAUSED BY SNAKE VENOM *

By W. H. Glass, M.D., *Hartford, Connecticut*

The venom of the water moccasin snake (*Ancistrodon piscivorus*) is used with some frequency in a heterogeneous group of diseases manifesting excess bleeding. Pecke and Rosenthal [1] reported enthusiastically about its beneficial effects in epistaxis of long standing, excess uterine bleeding, Osler's disease (hereditary hemorrhagic multiple telangiectasis), and various forms of purpura based on either toxic, allergic, or endocrinal abnormality. They state categorically that there are no contraindications to snake venom therapy. The venom was given subcutaneously for systemic effects in their series of cases, as has become the accepted procedure.

The venom of the Fer-de-lance (*Bothrops atrox*) is packaged and used for local hemostasis in instances where bleeding surfaces are readily available and where excessive bleeding can be anticipated, as following dental extraction or tonsillectomy. It is felt that snake venoms, in general, precipitate the clotting mechanism and do not require the action of thrombokinase, calcium, or prothrombin for the coagulation of fibrinogen to fibrin.

The venom of the cobra is used clinically as an analgesic. Macht [2] summarizes the work done in this field using cobra venom as a post-operative analgesic and in pain-producing malignancies. He has had no instances of toxicity, except slight to moderate discomfort at the site of the injection, and feels that its efficacy is greater than the opiates or the newly developed synthetic narcotics. In no instance has he had to discontinue the use of the drug because of untoward reactions.

Physiological research in reptile and insect venom has shown adverse effects following large dosages . . . comparable to the dose injected by the animal in the act of defending itself or in the act of food-seeking. Essex [3] gives a detailed review of the effects on circulation and the variable degrees of heart block in various experimental animals. In no instance was tachycardia produced. Brown,[4] in investigating the effects of water moccasin venom in large doses on dogs, shows that "there is a definite relationship between the quantity of venom injected and the cause of death: the heavier doses yield the neurotoxic (central) effects and the lighter doses yield the 'shock' (peripheral or circulatory) effects." Further work [5] by the same investigator shows that strong venom solutions slow the heart initially by action on the vagus mechanism, probably the ganglion cells. This effect can be abolished by atropin. The latter conclusions were arrived at following work on the isolated amphibious heart.

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It is to be understood that the amounts of venom used clinically to control bleeding, either topically or systemically, are minute in comparison to the amounts used by the animal itself or the amounts used in the above-mentioned experimental work.

A detailed search of the literature has yielded no instance of the type of reaction which occurred in the patient here reported.

Case Report

F. M., a white female, aged 22 at onset of present illness, was first seen in the summer of 1945 with a complaint of nervousness and palpitations. She gave a history of frequent severe nose bleeds for the past four years, which had been diagnosed three years ago as due to multiple small telangiectasia of the hereditary type on the nasal septum. Her family history included one sister and two brothers who had frequent epistaxis. They had all secured relief with snake venom. The patient had two sisters who had not manifested any bleeding. Her mother had severe nose bleeds and died at the age of 50 of "secondary anemia." Her maternal grandfather had bled, as had also a maternal uncle.

There had been no purpura or bleeding from the gums. Her menses were regular and lasted five to six days. There was a definite tendency for increased bleeding from her nose at the time of menses. In a diagnostic survey at the time of onset of excessive bleeding, a definite vasomotor rhinitis was also found, with hyper-reaction to various foods, pollen, and dust allergens. The consultant allergist felt that there was a definite relationship between the allergy and the onset of bleeding, as sneezing would undoubtedly be the most frequent beginner of massive epistaxis. A complete hematological survey, including coagulation time, bleeding time, and blood platelet count, was normal. The basal metabolic rate was minus 14 and an electrocardiogram showed an isoelectric T_3, otherwise being well within normal limits.

The patient was desensitized to dust and offending pollens, and was placed on an elimination diet. She was started on moccasin snake (*Ancistrodon piscivorus*) venom solution (Lederle), 0.4 c.c. subcutaneously, which was rapidly increased to 1.0 c.c. every four to six days. On this régime she had a prompt beneficial response with a marked diminution in epistaxis within three weeks, to a point of minor bleeding episodes at six- to eight-week intervals.

In February of 1944, approximately 18 months after onset of snake venom therapy, she noticed the insidious onset of nervousness, weight loss (20 pounds in seven months), menstrual irregularity, and rapid heart action. Repeated basal metabolic rates varied from plus 40 to plus 70. In September of that year, she was hospitalized and an initial basal reading of plus 66 was obtained, with a resting pulse rate at the level of 120. Hematological studies and urinalysis were negative. Blood cholesterol determination was not done. She was lugolized with a decrease in her basal rate to plus 11, within two weeks following which a subtotal thyroidectomy was done. At no time did she have a palpable struma nor any of the eye signs of hyperthyroidism. The pathological report showed two encapsulated masses of thyroid tissue which, on microscopic examination, showed some increase of connective tissue but no evidence of hyperplasia.

Following the thyroid resection she continued to be nervous and emotionally upset, with a continued tachycardia. She noticed that she had a tendency to gain weight, despite a low food intake. Four months following thyroidectomy she was given Lugol's solution, 10 minims three times a day for 60 days, with no apparent effect. At the end of that time a blood cholesterol determination showed a reading of 240 mg. per cent. Throughout this time she had continued snake venom as previously outlined.

At the time of initial examination here, she was badly upset emotionally, moderately obese, and with a continuous tachycardia at the level of 150. Blood and

urine examinations were essentially normal. Her basal rate was plus 41 per cent. General examination was negative, except for a thyroidectomy scar. No underlying thyroid tissue could be palpated. Physical examination and fluoroscopy of the heart showed only a tachycardia. Electrocardiogram showed a regular sinus rhythm with a rate of 140. There was slurring of the QRS complex in limb Lead I, and in precordial leads CF_2 and CF_4. There were no essential variations in either intervals, rate or tracing contour in various positions, or during unilateral or bilateral carotid sinus massage. The initial impression here was a supra-ventricular tachycardia of undetermined etiology. The patient was placed on quinidine sulfate grains 3 four times a day. Following eight days of this medication there was a slight decrease in pulse rate, but within one more week she had returned to the original status, and had begun to present signs of heart failure manifested by dyspnea at rest and transient ankle edema. At this time she was placed on thiouracil, 0.2 gm. three times a day. This had to be decreased because of nausea, and then continued in lesser amounts. Following three weeks of this therapy there was no significant variation and the thiouracil was discontinued.

At this time, the patient was re-hospitalized for further study. She presented a moderate secondary anemia, early manifestations of multiple vitamin deficiencies, a basal metabolic rate of plus 31, and a blood cholesterol of 175 mg. per cent. Snake venom was discontinued. Large amounts of enteral and parenteral vitamin preparations were given, and the patient was urged to increase her grossly deficient food intake. Within two weeks she began to have increased nasal bleeding and had to be fulgerated topically. Shortly after this, 21 days after the discontinuance of snake venom, she developed a full-blown picture of myxedema with a normal heart rate, gross obesity and a classical distribution of cutaneous edema. Her basal metabolic rate decreased to minus 32. She was placed on desiccated thyroid tissue orally, which had to be increased to 20 to 25 grains per day to bring her to a normal metabolic status. Now with periodic nasal mucous membrane fulgeration, and intensive anti-allergic measures, she has occasional minor bleeding episodes, but is otherwise asymptomatic.

Summary

An instance of familial hereditary hemorrhagic telangiectasis is presented that was treated with snake venom for massive epistaxes. She responded satisfactorily, with a diminution in her nasal bleeding. She developed, however, a syndrome simulating hyperthyroidism sufficiently closely to warrant thyroidectomy. This operation did not halt the progress of the disease. With the discontinuance of snake venom the entire picture changed to post-operative myxedema. Her nasal bleeding has been kept under control by fulgeration. This is the first instance of this type of response recorded. One is unable to tell whether allergy is a responsible factor or whether this is a drug idiosyncrasy.

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STILBAMIDINE IN THE TREATMENT OF HISTOPLASMOSIS: TWO CASE REPORTS*

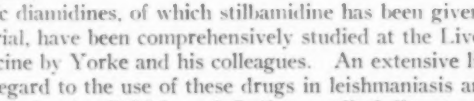
By JOHN H. SEABURY, M.D., *New Orleans, Louisiana*

To date, no definitely effective therapeutic agent has been reported for use in histoplasmosis. Isolated instances of apparent improvement or cure following the use of various drugs and physical agents have been published. The final outcome of these cases is, for the most part, not to be found in the literature. The author believes that when hopeful reports are published, particularly in relation to new drugs, the experience of others with these agents should be reported, even if the results are unfavorable. Otherwise, considerable duplication of negative results must occur.

Among the more recent drugs to receive tentatively favorable comment is stilbamidine. Parsons and Zarafonetis[1] state that, to their knowledge, two cases of histoplasmosis have been treated with stilbamidine, both in conjunction with an antimony preparation. One is reported to have shown "striking improvement"; treatment in the second case was unsuccessful. Seabury and Artis[2] reported that in vitro susceptibility studies suggest that stilbamidine is the most effective histoplasmocidal agent of the more commonly used drugs and antibiotics. The present report deals with two patients with histoplasmosis who were treated with stilbamidine.†

The aromatic diamidines, of which stilbamidine has been given the most thorough clinical trial, have been comprehensively studied at the Liverpool School of Tropical Medicine by Yorke and his colleagues. An extensive literature has accumulated in regard to the use of these drugs in leishmaniasis and trypanosomiasis, particularly in the British and Indian medical literature. Stilbamidine seems to be an acceptable therapeutic agent for the treatment of kala-azar and Rhodesian trypanosomiasis. More recently the diamidine drugs have been given a clinical trial in multiple myeloma.

Chemically, stilbamidine is 4–4′ diamidinostilbene



Its mode of action on the Trypanosomidae is not definitely known, but it is believed by some to have a direct action on the organism. The single dose level generally used in kala-azar varies from 1 mg. per kg. of body weight to 3 mg. per kg. of body weight. The frequency of administration in reported cases of leishmaniasis has differed considerably. At present, the most common schedule seems to be the administration of a single dose every day or every other day. It may be given in courses totalling about one gram per 100 pounds of body weight, or continuously, in severe cases, to a much larger total dose. Because of its property of irritation, stilbamidine is given preferably by the intravenous route although intragluteal administration may be used.

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From the Department of Internal Medicine, University of Michigan Medical School.

† The stilbamidine used was obtained from Merck & Co., through the courtesy of Dr. D. F. Robertson.

Case Reports

Case 1. The first patient to be treated with stilbamidine was a 23 year old Negro, who was admitted to the Michigan Rapid Treatment Center on March 6, 1945. This man had developed a small penile sore in February of 1942. The blood serology at that time was negative, and remained so when repeated in August 1942, January 1943, and March 1943. Despite this fact and the chronicity of the lesion, a physician made a presumptive diagnosis of primary syphilis and administered four injections of neoarsphenamine. Despite some improvement in the appearance of the ulcer, the patient discontinued treatment. No further therapy was received until after his admission to the Rapid Treatment Center.

During the interval of two years between the administration of neoarsphenamine and his admission to the Center the lesion had increased in size very slowly, and on occasion was moderately painful. The sole constitutional manifestation of illness was a 10 pound weight loss.

On admission to the Rapid Treatment Center, the penis presented a secondarily infected ulceration of the glans and prepuce. Induration was slight, and tenderness minimal. Bilateral inguinal lymphadenopathy was present, the nodes being slightly enlarged, discrete, and rubbery to palpation. Neither the liver nor spleen was palpable. A chest roentgenogram appeared normal.

Thorough laboratory study revealed no evidence of syphilis, chancroid, lymphopathia venereum, or granuloma inguinale. Urinalysis was normal. The hematological examination was normal except for a slight leukopenia, 4,900 cells per cu. mm., and a differential count showing 44 per cent neutrophilic granulocytes, 37 per cent lymphocytes, 16 per cent monocytes, and 3 per cent eosinophiles. The total serum proteins were 8.7 gm. per cent with an A–G ratio of 1. Biopsies taken from the penile ulcer and the inguinal lymph nodes were diagnosed as histoplasmosis. Blood agar cultures made from this material yielded a growth of *Histoplasma capsulatum*. The histoplasmin skin test was negative.

Because of his excellent general condition, and the presence of a local lesion whose progress could be followed with ease, it was decided to treat him with stilbamidine. Local application of penicillin was used for a short time to aid in overcoming the secondary infection. Potassium permanganate soaks, 1:8,000, were occasionally used for the same purpose. Stilbamidine was administered intravenously in the amount of 2.5 to 3.0 mg. per kg. of body weight per injection. The drug was prepared in distilled water.

From April 12, 1945 until May 9, 1945, he received a total of 3,534 mg. of the drug. He was then discharged for a rest period, and was readmitted on June 13 of the same year. From this latter date until August 14, 1945, he was given a total of 3,923 mg. of stilbamidine. The administration of the second course was delayed and hampered by severe urticarial reactions which appeared to be allergic in nature. However, when the method of preparing the solution was changed, and it was stored only for a day or two in a brown glass bottle, no further difficulty was experienced.

At the time of discharge, the lesion had improved in appearance. Local edema had decreased, and some degree of epithelialization was present. However, he had experienced moderate anorexia, occasional headache, and slight weight loss. The total white blood cell count was now 3,950 per cu. mm. His general physical appearance was not as good as on his first admission. Just prior to discharge from the hospital, the penile lesion was again biopsied. *Histoplasma capsulatum* were found in abundance. There was neither pathological nor clinical evidence that stilbamidine had exerted a significant therapeutic effect. He was afebrile throughout both hospital admissions. The total dose of stilbamidine which he received was 7,457 mg.

Case 2. The second case to be given stilbamidine was a 61 year old white male, who was first seen in the Otology Clinic of the University Hospital on April 3, 1945,

complaining of hoarseness and difficulty in breathing. Hoarseness had been progressive for more than a year prior to his first visit. Laryngeal pain had been present for nine months, dyspnea and wheezing for two months. Dysphagia began in February, 1945, and was progressive until the time of admission. A 20 pound weight loss had occurred during the year. Neither cough, hemoptysis, chest pain, nor fever had been present.

Physical examination revealed poor oral hygiene, an S-shaped deformity of the nasal septum, and a polypoid mass obstructing a view of the true vocal cords. There was no ulceration of this mass. There was no lymphadenopathy, and neither the spleen nor liver was palpable. A chest roentgenogram was normal.

Laboratory studies, including total and differential white blood cell count, were entirely normal. Sigmoidoscopic examination, to a level of 25 cm., was negative. The Kepler water test was normal. Histoplasmin skin test was negative, but a histoplasma vaccine (yeast form), given intradermally, produced a pruritic papule which persisted for days and became slightly pigmented.

On April 4, 1945, laryngeal biopsy and tracheotomy were performed. This biopsy showed enormous numbers of *Histoplasma capsulatum*. A swab from the tracheotomy tube was streaked on blood agar slants on April 13. These cultures gave bacteriological confirmation of the diagnosis of histoplasmosis.

The administration of intravenous stilbamidine was begun on April 10, 1945. A single dose level of 2 mg. per kg. of body weight was selected. After 11 injections the patient was allowed a week of freedom following which the use of the drug was resumed.

Visualization of the larynx on May 12 was reported as showing much less inflammation than previously and some decrease in size of the lesion. The patient was then discharged. He had received a total of 2,000 mg. of stilbamidine.

Ten days later he was readmitted for further treatment. At this time the examiner thought there had been considerable shrinkage of the granuloma. A more adequate airway was now present. From May 23 until June 7 he received 11 intravenous injections of stilbamidine, a total of 1,400 mg.

This patient was next seen on July 9, 1945, at which time he complained of increased ease of fatigue, excessive flow of mucus from his mouth and tracheotomy tube, and some slight bleeding from the tube. Laryngeal examination was reported as showing some increase in the extent of the granuloma. He was admitted for a third course of stilbamidine therapy. During this admission he was given 12 more injections, a total of 1,500 mg. for the course.

Two months later, September, 1945, the patient returned stating that he had eaten and slept well, and felt generally improved. Examination of the larynx showed some edema of the epiglottis and arytenoids. There was slight roughening in the region of the cords. The airway was still diminished in size, but its appearance was better than when previously seen. It was then decided to observe the patient without further therapy, the opinion being that he had shown improvement.

It is notable that he was afebrile during all these hospital admissions with the exception of two days on which he underwent operative procedures. On these two occasions his temperature was elevated to 101° F.

Because of increasing pain in the eyes and frontal region, he was readmitted on October 18, 1945. His cough had become more constant and more productive. Laryngeal examination showed a definite increase in the activity of the disease. The hemoglobin had fallen to 12.3 gm. per 100 ml. of blood, and the total white blood cell count had risen to 11,250. He was given 11 daily injections of stilbamidine, a total of 1,375 mg. for the course, and was then discharged.

His condition continued to deteriorate while at home and following five rather severe hemorrhages from around the tracheotomy tube he was readmitted on Decem-

ber 27, 1945. His neck was swollen and presented a firm, hot, red, pulsating mass anterior to the sternocleidomastoid muscle and just superior to the right clavicle. The mass was fluctuant. Massive edema of the epiglottis and aryepiglottic folds was present. His temperature fluctuated between 101° F. and 103° F., for three days prior to incision and drainage of the neck abscess. Following drainage, he was afebrile for one week but then showed frequent elevations of his temperature, not exceeding 100° F. The total white blood cell count was normal, but the differential revealed 13 per cent monocytes. During this admission he suffered one moderate hemorrhage from the nose and mouth. Paresthesias in the trigeminal distribution were present bilaterally, both corneal reflexes were absent, a corneal ulcer was present O.D. A tarsorrhaphy was performed on the right. A chest roentgenogram taken during this admission showed no active pulmonary disease. He was discharged to the Wayne County Infirmary for terminal care on February 8, 1946.

From February 8, 1946 until his death on April 11, 1946, his course was simply one of progressive respiratory distress and recurrent bleeding from the tracheotomy tube. His temperature fluctuated between 99° and 101° F. No autopsy was obtained. He had received a total of 6,275 mg. of stilbamidine.

SUMMARY

A report is given of the response of two patients with histoplasmosis when treated with stilbamidine. Insufficient data are available to evaluate the adequacy of the total dose given to these patients. Factors of drug fastness or increasing resistance are not known, and it may be that an interrupted series of injections was chosen unwisely. However, both patients received a total dose at least equal to the average reported for the treatment of kala-azar and trypanosomiasis, and the method of administration has been used widely. One patient exhibited a toxic manifestation of the drug, cranial nerve palsy (trigeminal).

Both of the patients in this report showed several features of histoplasmosis which do not seem to be known generally. Histoplasmosis is not infrequently a localized granuloma which remains such for relatively long periods of time. When the disease is recognized before the patient is aware of constitutional manifestations of disease, there is often no fever, hepatomegaly, splenomegaly, anemia, or leukopenia. Neither of these patients reacted to skin-test doses of mycelial histoplasmin and neither had infections of a type which might induce a state of anergy. The histoplasmin used was known to be active. One of the patients did react to a heat-killed vaccine made from the yeast form of the organism.

Although both patients were regarded initially as demonstrating improvement while under treatment with stilbamidine, this was temporary and the drug could not be said to have modified the course of the disease to a significant degree.

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EDITORIAL

NEW LIGHT ON THE PHARMACODYNAMICS OF HEART FAILURE

SINCE Withering [1] established the empirical fact that the powdered leaves of foxglove were a valuable remedy for the dropsy, many of the pharmacological actions of digitalis have been elucidated. Those that have gained general acceptance are well summarized by Willius [2] in three main compartments:

(a) digitalis depresses the function of the sino-auricular and the auriculo-ventricular nodes, and a tendency to slowing of the cardiac rate results;
(b) it depresses conduction throughout the cardiac muscle, particularly through the auriculo-ventricular bundle, and increases the refractory period in both the auricles and ventricles;
(c) it increases the amplitude of cardiac contraction and tends to restore tonus, apparently through a direct action on the heart muscle.

The therapeutic applications of digitalis are each based on one or more of these accepted actions. Thus, in auricular fibrillation it is effective by depressing AV conduction, with consequent slowing of the ventricles. In sinus tachycardia, on the other hand, if it acts at all to slow the heart, it functions by increasing vagal tone and depressing the SA node. In congestive heart failure many actions have been ascribed and disputed. Mackenzie and Lewis both considered that slowing the heart's rate was the important action. It has also been widely thought to exert its main effect by a direct action on the myocardium, either by increasing the force of systolic contraction or by increasing diastolic tonus, or by both. Recent experimental work has cast doubt on all these concepts, and the whole question of digitalis action in heart failure has again been haled into court. Evidence is fast accumulating that its chief action is exerted elsewhere than on the heart itself.

As long ago as 1926 Harrison and Leonard [3] showed that digitalis lowered the output of the heart in normal dogs. Dock and Tainter in 1930 [4] demonstrated that the venous pressure was also lowered in normal dogs by digitalis. They showed that this venous depressor action was the result of constriction of the hepatic veins, with trapping of blood in the liver and consequent diminution of the venous return. They suggested that a similar

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[3] HARRISON, T. R., and LEONARD, B. W.: The effect of digitalis on the cardiac out-put of dogs, and its bearing on the action of the drug in heart disease, Jr. Clin. Invest., 1926–1927, iii, 1.
[4] DOCK, W., and TAINTER, M. L.: The circulatory changes after full therapeutic doses of digitalis, with a critical discussion of views on cardiac output, Jr. Clin. Invest., 1930, viii, 467.

mechanism might be at work in man. Rytand [5] in 1933 demonstrated that digitalis lowered venous pressure in normal man, and Wood [6] in 1940 showed that the drug reduced venous pressure in patients with heart failure, independently of any change in heart rate. He also adduced evidence against the hepatic vein "throttle" mechanism suggested by Dock and Tainter a decade earlier.

Forssmann's technic of intracardiac catheterization,[7] developed by Cournand and Ranges in 1941,[8] has afforded a new, easy and accurate method of obtaining serial readings of right auricular pressure and cardiac output. This method gives fair promise to settle the long disputed mechanism of digitalis action in congestive failure. McMichael and his colleagues, at the Postgraduate School in London, have been the first to take advantage of this technic, and the results of their early investigations were published in 1944.[9] They first made 25 series of observations on a group of 24 patients; three of these had normal hearts, while the remainder suffered from some form and degree of heart failure. The diseased group included patients with hypertensive, valvular and coronary disease, and others with anemia, cor pulmonale and thyrotoxicosis. The one constantly observed effect of 1.5 mg. digoxin administered through the catheter was a fall of right auricular pressure. This occurred in each and every patient, in the normals and in those with cardiac failure alike. Cardiac output, on the other hand, behaved variously: it rose in 15, it fell in seven, and in three there was no significant alteration. Scrutiny of these results showed that there was a nice correlation between the initial level of output, and its response to digoxin. Thus, those patients whose output had been normal or high before digoxin was administered, showed a fall in output after digitalization; this group was composed of the normal patients and those with cor pulmonale and anemia. On the other hand, those who had a low initial output responded to digoxin with a rise in output; this larger group contained the hypertensive, valvular, coronary and thyrotoxic failures. Twelve further cases with a low initial output have subsequently been studied and reported.[10] In all of these also, the right auricular pressure fell while the output rose significantly after digoxin.

From this analysis the authors introduce the concept of "High Output" and "Low Output" failure. They propose that high output failure is caused by conditions which demand an increase in the output of the heart, such as

[5] Rytand, D. A.: The effect of digitalis on the venous pressure of normal individuals, Jr. Clin. Invest., 1933, xii, 847.

[6] Wood, P.: The action of digitalis in heart failure with normal rhythm, Brit. Heart Jr., 1940, ii, 132.

[7] Forssmann, W.: Die Sondierung des rechten Herzens, Klin. Wchnschr., 1929, viii, 2085.

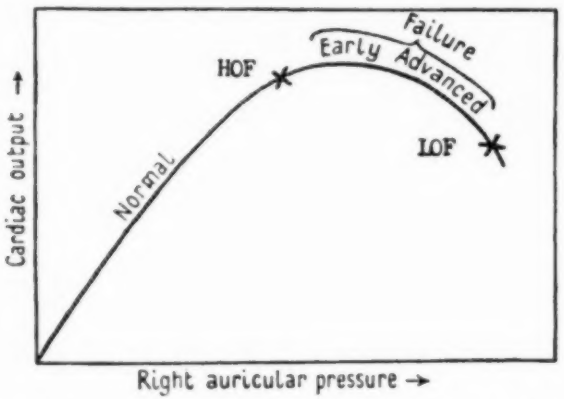
[8] Cournand, A., and Ranges, H. A.: Catheterization of the right auricle in man, Proc. Exper. Biol. and Med., 1941, xlvi, 462.

[9] McMichael, J., and Sharpey-Schafer, E. P.: The action of intravenous digoxin in man, Quart. Jr. Med., 1944, xiii, 123.

[10] Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Effects of venesection in low output heart failure, Clin. Sci., 1946, vi, 41.

anemia, emphysema, beriberi and arteriovenous aneurysms. In this form of failure the high venous pressure is a compensatory mechanism, called into play to maintain the required high output. Whereas in the more common low output failure caused by hypertensive, valvular or coronary disease, the high venous pressure is the result of back-pressure behind the failing ventricles.

To explain the mechanism of these two types of heart failure McMichael appeals to Starling's curve:



The heart in advanced congestive failure with a diminished output, is situated on the "overloaded" part of the curve; that is, at a point where the heart can no longer respond to increased venous filling by increasing its output. This may be represented by the hypothetical point LOF. The heart in high output failure, in contrast, is on the upstroke of the curve near its summit (at the hypothetical point HOF). Such a heart is still responding gallantly to the demand for high output.

Now any measure which reduces venous pressure will tend to draw the heart's status back along the curve from right to left; in other words, if the heart begins at LOF and travels along the curve to the left, its output will be increased; whereas, if its starting point is HOF, the output will be diminished.* And this is exactly what was found to occur with intravenous digoxin. From this McMichael suggests, logically enough, that the primary action of digitalis is to reduce venous pressure. How it acts to produce a fall in venous pressure is a matter for speculation; McMichael proposes tentatively, as the most plausible explanation, a "relaxation of venomotor tone."

* It is convenient here to represent both forms of failure on the same curve. But it should be pointed out that, in reality, the curves for each form are set at a different level of output. In other words, although the shape of the curves for each is approximately the same, a heart in low output failure, as it is "pulled back over the hump of the curve" from LOF, is not likely to exceed 4 or 5 liters in minute output; whereas the point HOF, referring to a heart in high output failure, represents an output of perhaps 7 or 8 liters per minute.

It could be argued that in low output failure, the fall in right auricular pressure which follows digitalization is the result and not the cause of the improved output—the output rising as a result of the stimulating action of digitalis on the ventricular muscle. The authors, therefore, investigated the effect of congesting cuffs to the thighs and venesection,[10] both of which measures must operate primarily by reducing venous filling pressure. They found that in four patients subjected to congesting cuffs, and in 10 subjected to venesection, the same augmentation of cardiac output occurred as was observed to accompany a similar reduction of right auricular pressure by digitalis. This finding shows that simple reduction of venous pressure is enough to increase output, and therefore makes it at least unnecessary to hypothesize that the reduction in venous pressure is the result of increased output. Against the belief that digitalis acts as a stimulant of heart muscle, McMichael quotes the work of Katz and his associates[11] who showed that digitalis had no effect on the contractility of isolated dog myocardium.

In this connection it is interesting to notice that many pharmacological experiments on the effects of glycosides on cardiac output have been made with strophanthin. Results obtained with this drug have sometimes been assumed to hold true for digitalis. It is therefore intriguing to find that McMichael claims,[12] as a result of his clinical experiments, a decided difference in the effects of the two glycosides, digoxin and g-strophanthin, on venous pressure and cardiac output. The difference is beautifully illustrated in emphysema hearts. In these cases (high output failure) digoxin reduced the right auricular pressure and with it, in most cases, the cardiac output was lowered[13]; whereas strophanthin often increased the output without having any appreciable influence on the right auricular pressure. He concludes that, while the primary and principal action of digoxin is to reduce venous pressure, that of strophanthin is to stimulate the myocardium. This may prove to be a point of clinical value, for, while digitalis may be ineffective in cor pulmonale,[14] and even actually harmful, strophanthin may be of definite benefit.

There are other interesting facets to McMichael's work. He has confirmed the point made by Wood[6] that slowing of the heart by digitalis is an insignificant factor in the control of congestive failure. Wood showed that the venous pressure continued to fall in response to digitalis, even if the heart rate increased as a result of some coincident stimulus (a full bladder, atropine). McMichael has gone further and demonstrated that in failure, with either sinus rhythm or auricular fibrillation, the venous pressure falls and the cardiac output increases after digitalis, even if the heart rate increases

[11] KATZ, L. N., MENDLOWITZ, M., and KAPLAN, H. A.: Action of digitalis on isolated heart, Am. Heart Jr., 1938, xvi, 149.

[12] MCMICHAEL, J.: The pharmacology of the failing heart, Brit. Med. Jr., 1948, ii, 927.

[13] HOWARTH, S., MCMICHAEL, J., and SHARPEY-SCHAFER, E. P.: Effects of oxygen, venesection and digitalis in chronic heart failure from disease of the lungs, Clin. Sci., 1947, vi, 187.

[14] VAQUEZ, H., and LUTEMBACHER, R.: De l'Ouabaine Arnaud, Presse méd., 1928, xxxvi, 129.

significantly. In one notable instance of hypertensive failure, where an urge to urinate accelerated the heart rate from 105 to 134 after the digoxin had been administered, the right auricular pressure meanwhile fell from 8 cm. to 0 cm. saline, while the output climbed from 3.05 to 5.3 liters per minute.

Again he has shown that, whereas venesection and digitalis each produce similar effects on venous pressure and cardiac output, the arterial blood pressure falls with venesection but frequently rises after digoxin. Thus, although output is increased to a similar degree after both procedures, it is evident that the heart is performing more work after digitalis than after venesection. With strophanthin the pressor effect was even more pronounced and the calculated work performed by the heart even greater.

Applying their new technic to the investigation of theophylline ethylene diamine (aminophylline), McMichael and his co-workers obtained further interesting results.[15] They found that, when 0.48 g. aminophylline was administered intravenously to patients with hypertensive failure, the venous pressure and the cardiac output responded in the same way as to digoxin—the venous pressure fell while the cardiac output rose. These effects occurred within five minutes in contrast with the digoxin effects which required an average of 20 minutes for their development; the cardiac output increase was also much greater than after digitalis. These aminophylline effects, however, were shortlived by comparison. Aminophylline, therefore, may be of the greatest value where a decrease in right auricular pressure is urgently needed; and, used in close succession with digitalis, a desirable summation of effects may be obtained.

Thus the technic of right heart catheterization for the estimation of cardiac output constitutes a significant advance in cardiological method. It has not, however, proved to be an open sesame to the pharmacodynamic problems of the failing heart. Though it has greatly advanced our knowledge, it has also revealed unrealized complexities.

In many of his experiments the small number of patients involved may well be said to render McMichael's work inconclusive. Certainly it is desirable that it be confirmed by other workers, and that much comparative work on larger series of patients should be done. The pioneer work that he has accomplished, however, is ingenious and challenging, and its significance cannot be doubted. He may well be on the way to justifying the editorial comment he has already received [16]—"he is at long last obtaining the final answers on the question of drug action." There is indeed much to be learnt from his investigations; but, for the moment, we must beware of applying his findings too closely to everyday practice. It is possible that the action of a full digitalizing dose of digoxin delivered abruptly into the right auricle may differ importantly from the effect of a quietly cumulative assimilation of digitalis via the portal system.

H. J. L. M.

[15] Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: The circulatory action of theophylline ethylene diamine, Clin. Sci., 1947, vi, 125.
[16] Leading Article, Brit. Med. Jr., 1948, ii, 947.

REVIEWS

Regional Ileitis. By BURRILL B. CROHN, M.D., Consulting Gastroenterologist, Mt. Sinai Hospital, New York. 229 pages, 14.5 × 22 cm. Grune and Stratton, Inc., New York, N. Y. 1949. Price, $5.50.

It is a pleasure to review this volume for it not only represents the first book on the subject of "Regional Ileitis" but it comes from the rich experience of a pioneer observer of the disease. Although the condition has ofttimes been referred to as "Crohn's" disease, the author, in all modesty, uses only the designation "regional ileitis." The book represents 18 years of careful study and analysis of 298 cases of regional ileitis in all its forms. No wonder, then, that a clear cut clinical picture evolves even though the etiology remains obscure. Certainly one can conclude as of now that regional ileitis is not related to tuberculosis and is clinically different from sarcoidosis. No single causative bacterial agency can be implicated with regularity.

The author discusses various theories regarding the pathologic mechanism in the creation of ileitis. For the first time a concept of the life cycle of the disease emerges. It is characterized by a consistent anatomical distribution, a typical clinical course, a progressive life history, typical complications (fistulas and obstruction) and favorable response to surgical treatment. In gross appearance, regional ileitis has definite characteristics that distinguish it from granulomas elsewhere in the alimentary tract. However, the histologic microscopy of the disease is non-specific. Crohn discusses two pathologic types suggested by Pemberton and Brown, (1) the localized group, which may and does progress to stenotic fibrosis, remains stationary and may lead to intestinal obstruction. This type is favorable to surgery; (2) the second group is scattered, progressive, in the nature of mucosal and submucosal lesions, and yields the majority of the disappointing end results of surgical intervention.

Under its clinical features, Crohn discusses those which are specific and those which are general. Most of the cases are not recognized until they have been symptomatic for one to five years or longer. This alone indicates how much the book is needed. The patients are not as toxic as those with ulcerative colitis. The two outstanding features in the physical examination of the cases of regional ileitis are: (1) an abdominal mass and (2) evidence of fistula formation, external and internal. The precise data on fistula formation in regional ileitis must be astonishing to physicians unfamiliar with the disease. Crohn makes the statement that, as a generalization, suppurative perianal fistulas in the presence of diarrhea indicate a pathologic process elsewhere in the intestinal tract. The course in regional ileitis is precisely analyzed; three variations in the course are considered.

The chapter on the roentgenologic study of regional ileitis has excellent illustrations. Early and late roentgen signs are mentioned and emphasis is placed on the string-sign as an almost pathognomonic finding. In many cases roentgenologic data of ileitis are completely missing and yet the clinical data are so convincing that the diagnosis must be adhered to in the absence of confirmatory roentgen signs. Actually, the diagnosis of regional ileitis is essentially a clinical one. The significance of the perianal fistulas cannot be overlooked.

Considerations regarding therapy pose an open question as to whether any conservative treatment is warranted. Crohn outlines the indications for such therapy. When it comes to surgical relief of the disease a complicated and rapidly changing picture is presented with the evidence favoring a single stage operation, namely, ileotransverse colostomy, with transection of the ileum, as a sufficient procedure to induce cure. However, there is a growing realization of the increasing evidence of recur-

rences following all types of surgical interference. It is clear also that surgery during episodes of acute regional ileitis is probably undesirable and most authorities favor expectant waiting and non-interference.

The section on ileo-jejunitis introduces the reader to the extraordinary possibilities of this disease and the frequently insoluble problems it presents. There is also a section on ileo-colitis (the combined forms of ileitis and colitis) which raises some puzzling problems.

The case reports are brief and to the point, the illustrations are exceptionally good and instructive, no words are wasted in the entire text.

In summary, this book is a must for all those internists who specialize in gastroenterology (and for others). It represents not only a concise presentation of 257 references from the literature but also Crohn's authoritative evaluation of his unusual experience with an important disease about which many of us have for a long time desired some clear cut conceptions.

SAMUEL MORRISON, M.D.

Medical Etymology, The History and Derivation of Medical Terms for Students of Medicine, Dentistry, and Nursing. By O. H. PERRY PEPPER, M.D. 263 pages; 15.5 × 24 cm. W. B. Saunders Company, Philadelphia. 1949. Price, $5.50.

The origins of our medical vocabulary are too often ignored. If more interest in the subject were encouraged, many of the philological absurdities which punctuate our "literature" would be avoided.

It may be argued that preciseness in the use of words is unnecessarily fussy; but it should be remembered that a word has only one excuse for its existence and that is its meaning. Violate its meaning and you snuff out its life—a crime for which Oliver Wendell Holmes coined the word "verbicide." It may also be complained that to have to learn the derivation of medical terms is to add an unnecessary burden to an already overloaded student. But this is not so. The cultural interest of such a study is in itself rewarding, and the reader must be duller indeed than the proverbial fat weed if he does not find intriguing the origins of such words as quinsy, tragus, ammonia, test tube, epithelium, and a hundred others; and, apart from this intellectual interest, the very practical advantage accrues that, if its root meanings are intelligently understood, a new terminology is much more easily learned and remembered.

Dr. Pepper has made a heroic bid to take the terrors out of etymology, and to interest students in the subject. No knowledge of Greek or Latin is necessary to derive benefit and pleasure from this excellent little volume. The author has produced an almost immaculate piece of lexicography in which there is little to criticize. The book is attractively printed and for a first edition there are remarkably few misprints. Words for discussion are grouped according to subjects, preclinical and clinical, so that the student may use each section in turn as he travels through the curriculum. An index at the back makes the book an easy work of reference.

The present reviewer would prefer to see Greek vowels given their proper quantities. The author has deliberately ignored these, for the same reason that he has refrained from using Greek characters—in the interest of simplicity. But there is as much difference between a short and a long "e" in Greek as there is between two other different vowels, such as "a" and "i," and such differences should be indicated To leave them out is to oversimplify at the expense of accuracy.

A score or so of words should, perhaps, have been more fully and interestingly dealt with; for example, one or more colorful points are overlooked in the treatment of such words as atlas, atropine, epiploic, anorexia, amyloid, lacrimal, jugular, hymen and morphia. It is surprising that the word "amphoric," with its picturesque derivation, is completely omitted. A number of minor inaccuracies are to be found, but only one real etymological blunder is apparent: the term for "absence of sweating"

is anidrosis and was used by Hippocrates; it is often spelt anhidrosis, because it comes from hidrōs, sweat. In medical writings today it is common to find it misspelt anhydrosis; but one is shocked to find that Dr. Pepper condones this spelling and derives the word from hydor, water. This is the more amazing because, in a later section, we find "hidrosis" and other words compounded from hidros correctly treated.

This is the first book of its kind that has appeared on the medical scene. Its conception is so laudable, and the standards of accuracy and clarity which the text for the most part maintains are so high, that it is beyond the range of serious criticism. It is a book which every student, without exception, should own. And many fully fledged physicians may wish to avail themselves of this handy text, feeling with propriety that many a medical

". . . word is too often profaned
For me to profane it."

H. J. L. M.

Diseases of the Liver, Gallbladder and Bile Ducts. 2nd Ed., revised. By S. S. LICHTMAN, M.D., F.A.C.P. 1135 pages; 15.5 × 24 cm. Lea and Febiger, Philadelphia. 1949. Price, $18.00.

This monumental compilation of the literature on diseases of the liver is the only work of its kind currently extant in the English language. It should, therefore, be carefully reviewed and appraised as a specialized textbook which presents the detailed statements of the findings of many authors. It is very valuable—particularly to those workers interested in finding out who wrote what about one phase or another of liver disease. However, the author has leaned over backwards in his desire to be complete and therefore frequently is contradictory in his statements. An example is the statement on page 425 that "Post-serum hepatitis is clinically indistinguishable from infectious hepatitis save for fairly consistent differences in the mode of onset"—compared with page 428, "The onset in an outbreak following yellow fever vaccination was almost indistinguishable from the infectious group."

In the discussion of liver abscess, the first cause is listed as bacillary dysentery, then the statement is made that the solitary liver abscess is often referred to as tropical liver abscess, and this in turn is due to amebic infection. The desire not to leave anything out leads to paragraphs such as that on page 536 where every conceivable factor is listed under "underlying causes" for cirrhosis—alcohol or syphilis figured in the majority of cases. In special types of cirrhosis, gall stones, chronic heart failure, Graves' disease, and abnormal blood pigments may operate as specific underlying causes. Other causative factors include tuberculosis, diabetes, infections including measles, scarlet fever, typhoid. . . . Perhaps most of the trouble here is in semantics—the use of the word "cause" instead of "frequently associated conditions."

And so one comes to the chief criticism. The author has not taken the time to make this a shorter book. There is no need for five pages of discussion of the supposed catarrhal origin of infectious hepatitis which the author correctly discards, and perhaps no need for a whole separate sub-heading on hepatolienal fibrosis of Banti's syndrome (page 673) when at the outset the author himself says it is presented for historical interest and the sake of completeness. This is particularly true since on page 585 the author has given a good summary of portal hypertension and its relation to splenomegaly, etc. Such things are, however, easier to find and criticize than cure, and should not be emphasized as against the general merit of this valuable compilation. It can be highly recommended as a source book and review.

F. B. B.

The Fundamentals of Pulmonary Tuberculosis and Its Complications, for the Student, the Teacher, and the Practicing Physician. Sponsored by the American College of Chest Physicians, Edited by EDWARD W. HAYES, M.D. 480 pages. Charles C. Thomas, Springfield, Illinois. 1949. Price, $9.50.

This book is an attempt by a group of doctors interested in diseases of the chest and active in bettering chest treatment to present the fundamentals of tuberculosis for the student, the teacher and the practicing physician. Taken all in all, the presentation is most interesting, although limitations of space have prevented the authors from going into sufficient detail for those seeking exact knowledge on a specific phase of the subject. For the beginning student, the detail is too great. However, many phases of tuberculosis are excellently presented in adequate detail. With so many contributors, there is bound to be some duplication, but in editing the overlapping has been held to a reasonable degree.

In a compendium such as this, some chapters are naturally outstanding. Among these are the sections on "Major Surgical Procedures," "Renal Tuberculosis," and "Diagnosis of Reinfection Pulmonary Tuberculosis." The views presented on the use of B.C.G. vaccine are not universally accepted, particularly the theory that it will produce a reinfection type of tuberculosis if persons immunized come in contact with the tubercle bacillus. Other well organized chapters are those on "Psychosomatic Aspects of Tuberculosis," "Public Health Aspects," "Pregnancy in Tuberculosis" and "Prognosis of Tuberculosis."

Those sections that deal with complications (enterocolitis, tuberculosis of the larynx) and anatomy could be improved upon, as could the addendum on streptomycin. In many chapters the discussion of streptomycin in its application to the particular phase of tuberculosis under consideration is quite scanty.

In spite of its often unavoidable defects, this is a book of distinct value. It is hoped that there will be future editions which will be better organized and which will keep the volume abreast of current developments in the subject.

L. H. H.

Psychosomatic Medicine: The Clinical Application of Psychopathology to General Medical Problems. 2nd Ed. By EDWARD WEISS, M.D., and O. SPURGEON ENGLISH. 803 pages; 15.5 × 23 pages. W. B. Saunders Co., Philadelphia. 1949. Price, $9.50.

It has been six years since the authors published the first authoritative text on Psychosomatic Medicine. Since then two things have happened: a great many fundamental studies have been made in this field; and the medical profession has become much more aware of its need to know more about this subject. The present edition is very welcome in that it includes much of the recent work in this field. It is entirely rewritten and is now a much more up-to-date text.

The book is practical in every respect. It is written in understandable language, free from the jargon that makes many psychiatric and psychoanalytic texts so difficult to read. As most physicians now realize, the subject of psychosomatic medicine is one they need to know more about if they wish to understand a large portion of the problems of their patients. The reviewer knows of no other text that can be so highly recommended for this purpose. The book is so authentic it can also be highly recommended to specialists in the fields of psychiatry and psychoanalysis.

This book serves two fundamental purposes. A careful study of it will enable physicians to understand more clearly the emotional and situational factors which contribute to the illness of many of their patients. But more important than this, it gives practical and concrete advice as to how physicians can treat the emotional problems of their patients in a more helpful manner.

H. W. N.

BOOKS RECEIVED

Books received during July are acknowledged in the following section. As far as practicable, those of special interest will be selected for review later, but it is not possible to discuss all of them.

Electrocardiographic Technique: A Manual for Physicians, Nurses and Technicians. By KURT SCHNITZER, R. T., M.D. 96 pages; 16 × 23 cm. 1949. Grune & Stratton, New York. Price, $3.50.

Industrial Toxicology. By LAWRENCE T. FAIRHALL, Scientist Director, Public Health Service, Federal Security Agency, etc. 483 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $6.00.

Industrial Toxicology. 2nd ed. By ALICE HAMILTON, M.D., Assistant Professor Emeritus of Industrial Medicine, Harvard School of Public Health, Boston, and HARRIET L. HARDY, M.D., Physician to the Division of Occupational Hygiene, Massachusetts Department of Labor and Industries, etc. 574 pages; 21 × 14 cm. 1949. Paul B. Hoeber, Inc., Medical Book Department of Harper & Brothers, New York. Price, $7.50.

Patología Psicosomática. By J. ROF CARBALLO. Prologo by PROF. C. JIMÉNEZ DÍAZ. 817 pages; 25.5 × 18 cm. (paper-bound). 1949. Editorial Paz Montalvo, Madrid, Spain.

The Skin Problem Facing Young Men and Women. By HERBERT LAWRENCE, M.D., Diplomate, American Board of Dermatology. 70 pages; 23 × 15 cm. (paper-bound). 1949. Timely Publications, San Francisco. Price, $1.50.

Stomach Disease as Diagnosed by Gastroscopy. By EDDY D. PALMER, A.B., M.S., M.D., Major, Medical Corps, United States Army. Formerly Chief, Gastrointestinal Section, Walter Reed General Hospital, Washington, D. C. 200 pages; 26.5 × 18 cm. 1949. Lea & Febiger, Philadelphia. Price, $8.50.

Treatment in Proctology. By ROBERT TURELL, B.S., M.D., Attending Proctologist, Hillside Hospital, etc. With a chapter on Psychosomatic Problems by LOUIS LINN, M.D. 248 pages; 23.5 × 15.5 cm. 1949. The Williams & Wilkins Company, Baltimore. Price, $7.00.

The Value of Hormones in General Practice. By W. N. KEMP, M.D., Vancouver, B.C. 115 pages; 27.5 × 21 cm. (loose-leaf, paper-bound). 1949. Burgess Publishing Company, Minneapolis. Price, $3.00.

You and Your Fears. By PETER J. STEINCROHN, M.D., F.A.C.P. Introduction by C. CHARLES BURLINGAME, M.D., F.A.C.P. 224 pages; 20 × 13.5 cm. 1949. Doubleday & Company, Inc., Garden City, New York. Price, $2.50.

COLLEGE NEWS NOTES

First ACP Regional Meeting, Puerto Rico

The first Regional Meeting of the American College of Physicians ever to be held in Puerto Rico is scheduled for October 16, 1949, under the Governorship of Dr. Rafael Rodriguez-Molina, F.A.C.P. The Puerto Rico Medical Association graciously put at the disposal of this meeting its buildings and facilities. An invitation is extended not only to the members and their friends in Puerto Rico but to other qualified physicians in the Island and to all members of the College from other countries and states. Dr. Hugh J. Morgan, current Regent and former President of the College, will attend the meeting as the official representative of the Board of Regents and will not only deliver a paper on the scientific program but will be Speaker of the Day at the Banquet in the evening, to be held at the Condado Beach Hotel.

The scientific program is as follows:

P.M.

2:00 Bleeding Tendency Due to Circulating Anticoagulants, with Report of a Case.
Eduardo R. Pons, Jr., M.D. (by invitation), and Mercedes Vicente de Torregrosa, Ph.D. (by invitation), San Juan City Hospital.

2:30 Pathogenesis of Schistosomiasis with Special Reference to Schistosomal Cirrhosis.
Enrique Koppisch, M.D., F.A.C.P., Acting Director and Professor of Pathology, School of Tropical Medicine, San Juan.

3:00 The Present Status of the Intradermal Reaction in the Diagnosis of Schistosomiasis and Filariasis.
Jose Oliver-Gonzalez, Ph.D. (by invitation), Associate Professor of Medical Zoology, School of Tropical Medicine, San Juan.

3:30 Myocarditis.
Hugh J. Morgan, M.D., D.Sc., F.A.C.P., Regent and Former President, The American College of Physicians; Professor of Medicine, Vanderbilt University School of Medicine; Physician-in-Chief, Vanderbilt University Hospital; Nashville, Tenn.

4:00 Incidence of Hypertension in Puerto Rico.
Ramon M. Suarez, M.D., F.A.C.P., Director, Mimiya Hospital; Consultant in Medicine, Veterans Administration Center, San Patricio Hospital; San Juan.

4:30 Electrocardiographic Changes in Phosphorus Poisoning.
Rubico S. Diaz-Rivera, M.D., F.A.C.P., Chief, Medical Service, San Juan City Hospital.

5:00 Treatment of Amebiasis with A.D. 4712.
Federico Hernandez-Morales, M.D., F.A.C.P., Associate Professor of Tropical Medicine, School of Tropical Medicine, and Enrique Perez-Santiago, M.D. (by invitation), Medical Supervisor, University Hospital, San Juan.

5:30 Meningitis in Infants and Children in Puerto Rico.
Antonio Ortiz-Ortiz, M.D., F.A.C.P., Chief, Pediatric Service, San Juan City Hospital.

6:00 Hypercholesteremia and Its Relation to Coronary Artery Disease.
Roberto Francisco Azize, M.D., F.A.C.P., Director, San Juan Diagnostic Clinic.

A.C.P. Postgraduate Courses

The American College of Physicians' Bulletin of Postgraduate Courses was published during July and distributed to all members of the College and to non-members on the mailing list.

Course No. 1, CARDIOLOGY, was given at the National Institute of Cardiology of Mexico, from August 15 to 26, with a registration of 25 physicians. Dr. William Dock, F.A.C.P., Professor of Medicine at Long Island College of Medicine, Brooklyn, was a Guest Professor from the United States, and Dr. George Morris Piersol, M.A.C.P., Secretary-General of the College, was the official representative of the Board of Regents. The course was unique in many respects inasmuch as it was organized so that all instruction was concluded at 1:00 p.m. daily, giving the rest of the day for sightseeing trips and a week-end for a more extensive trip to Taxco. The type or method of instruction was particularly suitable to older individuals who find close concentration on continuous didactic lectures tiring, in that this course provided an hour of didactic instruction followed by an hour in the wards and laboratories. All instruction was given in English and the whole course was conducted on a high plane of excellence.

Other courses on the schedule are:

Course No. 2, GASTRO-ENTEROLOGY, October 10–14, University of Chicago School of Medicine, Chicago, Ill., Walter L. Palmer, M.D., F.A.C.P., Director.

Course No. 3, CLINICAL NEUROLOGY, October 17–21, Jefferson Medical College of Philadelphia, Philadelphia, Pa., Bernard J. Alpers, M.D., F.A.C.P., Director.

Course No. 4, PRECLINICAL SCIENCE IN INTERNAL MEDICINE, October 24–29, Washington and St. Louis Universities, St. Louis, Mo., W. Barry Wood, M.D., F.A.C.P., and Ralph A. Kinsella, M.D., F.A.C.P., Directors.

Course No. 5, RECENT ADVANCES IN THE DIAGNOSIS AND TREATMENT OF CARDIOVASCULAR DISEASE, November 14–19, Massachusetts General Hospital, Boston, Mass., Howard B. Sprague, M.D., F.A.C.P., and Edward F. Bland, M.D., Directors. This course is definitely limited to 100 registrants. The course is more than half filled and it is probable that it will be over-subscribed with the result that few, if any, non-members can be accommodated.

Course No. 6, BIOLOGICAL AND PHYSIOLOGICAL APPROACHES TO INTERNAL MEDICINE, November 28–December 2, University of Wisconsin Medical School, Madison, Wis., William S. Middleton, M.D., F.A.C.P., and Karver L. Puestow, M.D., F.A.C.P., Directors. This course is registered to capacity and no new applications can be accepted.

Course No. 7, BLOOD DYSCRASIAS, December 6–10, Medical College of Alabama, Birmingham, Ala., James B. McLester, M.D., F.A.C.P., Director.

Course No. 8, THE PHYSIOLOGICAL APPROACH TO CLINICAL PROBLEMS IN THE CARDIOVASCULAR DISEASES, December 5–10, University of Southern California School of Medicine, Los Angeles, Calif., George C. Griffith, M.D., F.A.C.P., Director.

New Group of A.C.P. Research Fellows Begin Work

The following Research Fellows, selected by the Committee on Fellowships and Awards and the Board of Regents during November, 1948, are now launched on their program of work as indicated. The selection of Research Fellows for 1950–51 will take place at a meeting of the Committee and the Board of Regents on November 12–13, 1949.

Dr. Stefan S. Fajans—investigative work in the field of determination of physiological mechanisms capable of stimulating or depressing the Islets of Langerhans—under

the preceptorship of Dr. Jerome W. Conn, University Hospital, Ann Arbor, Mich.; began July 1, 1949, for a period of one year.

Dr. Horace W. Gerarde—for a study of the distribution of phosphorus compounds in leukocytes in different diseases, leukemia, infectious mononucleosis, multiple myeloma; also a study of the enzyme systems in these diseases by biochemical and histochemical technics; investigation of the organic phosphorus distribution in liver diseases—under the preceptorship of Dr. Nathan A. Womack, State University of Iowa College of Medicine, Iowa City, Iowa; began July 1, 1949, for a period of one year.

Dr. John C. Laidlaw—the Alfred Stengel Research Fellowship, a study on the metabolism of certain cholinesterase inhibitors in relation to myasthenia gravis—under the preceptorship of Dr. F. G. Young, University College, London, England; began July 1, 1949, for a period of one year.

Dr. James Metcalfe—a study on the dynamics of the circulation under various conditions—under the preceptorship of Dr. Eugene M. Landis, Harvard Medical School, Boston, Mass.; began July 18, 1949, for a period of one year.

Dr. Samuel M. Peacock, Jr.—to conduct study on the cytochemistry of nervous tissue during growth and other physiological activity—under the preceptorship of Dr. Robert Hodes at Tulane University of Louisiana School of Medicine, New Orleans, La.; began August 1, 1949, for a period of one year.

Dr. Jack L. Strominger—studies on the microchemistry of the brain tissue—under the preceptorship of Dr. O. H. Lowry, Washington University School of Medicine, St. Louis, Mo.; began July 1, 1949, for a period of one year.

Dr. Edgar Woody, Jr.—to continue studies on the combined effect of potassium iodide and streptomycin in experimental tuberculosis—under the preceptorships of Drs. Hugh J. Morgan, Hollis E. Johnson and Roy C. Avery at Vanderbilt University School of Medicine, Nashville, Tenn.; began July 1, 1949, for a period of one year.

Oklahoma Regional Meeting

The 1948 Regional Meeting of Oklahoma members of the American College of Physicians took place on September 9 at the University of Oklahoma School of Medicine at Oklahoma City, under the General Chairmanship of Dr. Wann Langston, F.A.C.P., College Governor for the State. A cordial invitation was extended also to members in Arkansas, Kansas and Texas. Dr. Mark R. Everett, Dean of the University of Oklahoma School of Medicine, addressed the group at lunch, and the guest speakers at the evening dinner meeting were Dr. Lewis J. Moorman, F.A.C.P., Oklahoma City, Secretary of the State Medical Association, and Dr. William S. Middleton, F.A.C.P., Madison, Wis., President-Elect of the College.

The following papers were presented at the scientific session.

Recent Advances in Liver Function Tests. Earl I. Mulmed, M.D., (Associate). Tulsa. Lower Nephron Nephrosis. Philip M. McNeill, M.D., F.A.C.P., Oklahoma City. Clinic. Minard Jacobs, M.D., F.A.C.P., Oklahoma City. The Insulins in Diabetes. A. W. Wallace, M.D., F.A.C.P., Tulsa. Experience with Hormonal Imbalance in Diabetic Pregnancies. Bert F. Keltz, M.D., F.A.C.P., Oklahoma City. The Differentiation of High Cord Lesions from Multiple Sclerosis. Alvin Rix, M.D., (by invitation), Oklahoma City. Newer Advances in the Knowledge of Sodium Metabolism and Its Application to Internal Medicine. John R. Taylor, M.D. (Associate), Kingfisher. Panel on the Use of Anticoagulants. Wann Langston, M.D., F.A.C.P., Oklahoma City; William S. Middleton, M.D., F.A.C.P., Madison, Wis.; F. Redding Hood, M.D., F.A.C.P., Oklahoma City; Frank Nelson, M.D., F.A.C.P., Tulsa. The Management of Meningitis. Carroll Pounders, M.D., F.A.C.P., Oklahoma City. Congenital Toxoplasmosis; with Report of a Case. J. Kenneth Thompson, M.D. (Associate), Fort Smith, Ark. Newer Advances in the Use of Antibiotics.

DOUGLAS M. GORDON, M.D., F.A.C.P., Ponca City. Collagen Fiber Diseases. WILLIAM S. MIDDLETON, M.D., F.A.C.P., Madison, Wis. Clinical Pathological Conference. HUGH JETER, M.D., F.A.C.P., Oklahoma City; FELIX PARK, M.D., F.A.C.P., Tulsa.

A.C.P. DIRECTORY, 1949

It had been anticipated that the new and revised Directory of the American College of Physicians would be ready for distribution on or about October 1, 1949. Some slight delay, unavoidable, due to termination of services of one of the editors, may be anticipated, but it is hoped that the Directory will be completed and delivered to all who placed orders therefor before November 1, 1949.

MEETINGS, A.C.P. COMMITTEE ON CREDENTIALS

The Committee on Credentials of the American College of Physicians will meet at the College Headquarters on November 12, 1949, and on or about March 18–19, 1950, and at Boston, Mass., on April 15, 1950.

Regulations of the Board of Regents prescribe that proposals of candidates must be filed sixty days in advance of action. This notice is published for the aid and direction of members who have candidates to propose.

TWENTY-SECOND GRADUATE FORTNIGHT OF THE NEW YORK ACADEMY OF MEDICINE

The Twenty-second Graduate Fortnight of The New York Academy of Medicine will be held at the Academy building, 2 E. 103d St., October 10–21, 1949, and the theme of the Fortnight will be "Advances in Diagnostic Methods." Dr. Louis J. Soffer, F.A.C.P., is Chairman of the Committee and Dr. Mahlon Ashford, F.A.C.P., of the Academy is the Secretary. Numerous other Fellows of the American College of Physicians are members of the Committee or are participating in the program. A comprehensive exhibit devoted to advances in diagnostic methods will form a part of the program. The registration fee is $5.00; programs are available through the Academy.

THIRD INTER-AMERICAN CONGRESS OF RADIOLOGY

The Third Inter-American Congress of Radiology will be held in Santiago, Chile, from November 11–17, 1949. The Government of Chile has lent the official patronage of the University of Chile. Hotel Crillon will be the headquarters. There are four main divisions of the program: "Radiological Exploration of the Cardiovascular System with Opaque Material"; "Diagnosis and Simple Radiological Explorations of the Skull"; "Radiation Treatment of Cancer of the Tongue"; and "Radiation Treatment of Cancer of the Cervix." Dr. James T. Case is the United States Regional Secretary of the Executive Committee. All communications concerning the meeting should be addressed to Room 1421, 55 E. Washington St., Chicago 2, Ill.

The 1950 Assembly of the Interstate Postgraduate Medical Association of North America will be held at the Hotel Stevens, Chicago, November 6–9, 1950.

The 12th Annual Symposium of the Duke Medical School will be held at Durham, N. C., Thursday, Friday and Saturday, October 13, 14 and 15. The general subject will be the "Basis of Disease." Among the guest speakers will be Drs. Stanley Brad-

ley, New York City, D. E. Clark, Chicago, John Dingle, Cleveland, Robert Elman, St. Louis, Paul Klemperer, New York, Joseph Lilienthal, Jr., Baltimore, C. N. H. Long, New Haven, William Parsons, Charlottesville, Hans Selye, Montreal and Robert Wilkins, Boston.

The American College of Physicians makes grateful acknowledgment of the recent subscription to Life Membership of Dr. Ernest W. Willetts, F.A.C.P., Pittsburgh, Pa.

Irvine H. Page, M.D., F.A.C.P., Cleveland, Ohio, has been elected President of the American Society for the Study of Arteriosclerosis.

Dr. Henry W. Woltman, F.A.C.P., Rochester, Minn., has been installed as President of the American Neurological Association.

Captain Joel J. White, (MC), U. S. Navy, a Fellow of the American College of Physicians, has been promoted to Rear Admiral and upon his own request was retired as of September 1, 1949, to accept the position of Medical Director of the University of New Hampshire, Durham, N. H. Admiral White had served 32 years on active duty and received a Citation under Actual Combat, Guadalcanal.

The American College of Physicians gratefully acknowledges the kindness of Maxwell Finland, M.D., F.A.C.P., Boston, in sending to the College Library of Publications by Members a bound Volume IV of his Collected Reprints, Nos. 154–218, for the period 1946–1948.

J. C. Geiger, M.D., F.A.C.P., Director of Public Health of the City and County of San Francisco, has recently been awarded the Order of the Star of Italian Solidarity by the President of the Italian Republic, for "great humanitarian activities for the Italian Republic and for the Italian citizens of San Francisco."

Major General R. W. Bliss, F.A.C.P., Surgeon General of the U. S. Army, has announced the appointment of Colonel Hugh R. Gilmore, Jr., F.A.C.P., to head the Pathology and Allied Sciences Division.

The following Fellows of the College were among the guest speakers at the 14th Annual Meeting of the Mississippi Valley Medical Society, which was held at St. Louis, September 28–30, 1949: Drs. Newell C. Gilbert, Louis N. Katz, Robert W. Keeton and Willard O. Thompson, Chicago; Dr. Lowell D. Snorf, Evanston, Ill.; Dr. William B. Bean, Iowa City; Dr. Seymour H. Rinzler, New York City; Dr. Oscar B. Hunter, Washington, D. C.; Dr. Henry H. Turner, Oklahoma City; Drs. Goronwy O. Broun, Llewellyn Sale and W. Barry Wood, St. Louis; Dr. Ovid O. Meyer, Madison, Wis.; and Dr. Francis D. Murphy, Milwaukee, Wis.

Drs. Edgar V. Allen, F.A.C.P., Rochester, Minn., Lewis M. Hurxthal, F.A.C.P., Boston, and Walter L. Palmer, F.A.C.P., are among the visiting lecturers at the 27th Annual Fall Conference of the Kansas City Southwest Clinical Society, October 3–6, 1949.

OBITUARIES

DR. WILLIAM GERRY MORGAN, M.A.C.P.

1868–1949

DR. WILLIAM GERRY MORGAN

With the sudden death of Dr. William Gerry Morgan, on the seventh of July, 1949, at Washington, D. C., the American College of Physicians lost one of its few remaining charter members. The news of his unexpected death brought deep sorrow to Dr. Morgan's many devoted friends in the College, particularly to those members of the Board of Regents and the Board of Governors with whom he had worked so intimately for so many years.

Dr. Morgan was born in Newport, N. H., on May 2, 1868. After completing his preliminary education at Fryeburg, Maine, he entered Dartmouth College, where he received his B.S. in 1890. Three years later he received his M.D. from the School of Medicine of the University of Pennsylvania, Philadelphia. After serving as Resident Physician at the Reading (Pa.) Hospital for one year, Dr. Morgan entered upon the private practice of medicine in Houston, Tex. He went to the southwest where the climate was less severe, because of his health. A year later, in 1895, he decided not to cast his lot with the growing community of Houston, but to return to his ancestral New England. Between 1895 and 1899 he carried on a private practice at Southport, Conn. The ambitious and energetic spirit of Gerry Morgan was not content with the limitations of a private practice in New England. After his health improved, he determined to devote his energies to the then newly developed specialty of Gastro-enterology. He entered upon a course of postgraduate work under Dr. Max Einhorn, F.A.C.P., at the New York Post-Graduate Medical School, following which he established himself in Washington, D. C. The wisdom of his decision was borne out by the successful career which he followed in that capitol city for half a century. It was not long after he moved to Washington before he was recognized as the outstanding Gastro-enterologist in that part of the country and a wise consultant. Professional recognition came to him when in 1904 he was appointed Professor of Gastro-enterology at Georgetown University School of Medicine, an appointment which he held with distinction throughout his entire life. He was Dean of the Medical School of Georgetown University from 1931–35, and in addition to this served as a Regent of the University for many years. Dr. Morgan's success in his special field of medicine was in no small measure due to the broad medical training which he obtained early in his career as a general practitioner. Although he was an ardent and enthusiastic student of Gastro-enterology, he never neglected the broader fields of medicine. Dr. Morgan was a Diplomate of the American Board of Internal Medicine. His success as a diagnostician was due to his skill in physical diagnosis, a keen understanding of patient psychology and an ability to properly evaluate modern diagnostic procedures in medicine. His interest in all phases of the practice of medicine, and particularly his personal attention to his patients were outstanding traits that dominated his professional life.

Dr. Morgan had never allowed the exacting demands of a large and important practice to interfere with his interest in the academic side of medicine. He was a con-

stant contributor to contemporary medical literature, writing about many aspects of Internal Medicine, other than Gastro-enterology. He contributed to many well known systems of medicine, including Tice's "Practice of Medicine," Prior's "Principles and Practice of Physical Therapy," Appleton's "The Fundamentals of Internal Medicine," "The Cyclopedia of Medicine" (F. A. Davis Company), Lippincott's "American System of Medicine," and "Principles and Practice of Therapeutics."

In recognition of his accomplishments, Dr. Morgan received the honorary degree of LL.D. from the University of Pennsylvania and from Georgetown University, and the degree of Sc.D. from Dartmouth College.

Few members of the medical profession ever took a more active part in organized medicine and medical societies than did Dr. Morgan. He served as President of the American Gastro-enterological Association (1913); the District of Columbia Medical Society (1919); the Clinico-Pathological Society (1919); the American Congress on Internal Medicine (1925); the International Medical Club (1930). He received one of his greatest honors when he was made President of the American Medical Association in 1930. Dr. Morgan also was an active member of the American Therapeutic Association, the Southern Medical Association (Councillor, 1924–28), the Medical Society of Virginia, Pan-American Medical Association, New York Academy of Medicine, Washington Academy of Science (Vice President, 1919), American Association of the History of Medicine, Washington Historical Society, Anthropological Society of Washington, American Archeological Association and the Association of Military Surgeons of the United States.

Of all the organizations to which Dr. Morgan gave his time and energy, there was none in which he took greater interest than the American College of Physicians from the day he was made a Fellow in 1916 until the end of his life. He showed his devotion to the College in many ways. In appreciation of his great personal contribution to the College, Dr. Morgan was made a Master in 1940. He served the College in many official capacities, as a Regent from 1916–20, as a Governor from 1929–32, as Secretary-General from 1932–37. His last official position was that of Vice-President, 1937–38. Because of Dr. Morgan's intimate personal acquaintance with the early history of the College and the outstanding role which he played in the reorganization and development of the American College of Physicians, he was selected as the College Historian. In this capacity, he worked indefatigably to collect the data which made it possible for him to edit the history of the College, published in 1940, entitled "The American College of Physicians—Its First Quarter Century."

Although Dr. Morgan dedicated his life to the practice of medicine, he was unusual in that he had a wide range of interests, law, dentistry, geology, farming, mechanics, photography and national politics—all had an appeal for him. To his other accomplishments, Dr. Morgan added those of a great sportsman. In spite of his busy life, he managed to find time, before his health placed restrictions upon him, to fish and hunt in many parts of the North American Continent. One of his greatest exploits was a hunting expedition to Alaska with his close friend and Fellow of the College, the late Dr. Harlow Brooks, of New York City. The experiences of this trip were recorded by Dr. Morgan in his entertaining account entitled "The Trail of a Cheechako in Alaska." He was an ardent fisherman, an expert with rod and fly, loving the swift streams and the quiet lakes. His camps and trails led far and wide, and he greeted the dawn in many entrancing spots. His summer home, "Hideaway," which for many years he maintained at West Springfield, N. H., was a tribute to his lifelong devotion to the New England of his youth. The charm of his New Hampshire residence was well known to many of his friends in the College who were fortunate enough to enjoy his generous hospitality and entertaining companionship. There are few men who ever brought to their work and their diversion greater enthusiasm and energy than did Dr. Morgan. His engaging personality, keen sense of humor, generous nature and

well balanced judgment earned for him the friendship and devotion of all who were thrown with him. The affection in which he was held was nowhere better exemplified than in the unfailing devotion which was shown him by all those who were associated with him in any capacity. His loss will be keenly felt and deeply regretted by his host of friends in all walks of life. No group, however, will feel his loss more keenly or miss him more than those who were privileged to work with him for so many years in the American College of Physicians. Dr. Morgan is survived by his widow, Mrs. Cora Morgan, and three daughters, Mrs. Myra Stump, Mrs. Ruth Hardison and Mrs. Gerry Wellborn, each of whom is the wife of a Rear Admiral in the U. S. Navy. The Officers, the Board of Regents, the Board of Governors and Fellows of the American College of Physicians extend to Dr. Morgan's family their heartfelt sorrow, over this irreparable loss which they have sustained.

GEORGE MORRIS PIERSOL, M.D., F.A.C.P.,
Secretary-General, ACP

DR. MAYO HAMILTON SOLEY

Born in Malden, Mass., April 14, 1907, Mayo Hamilton Soley was reared in the New England environment. He graduated from Bowdoin College in 1929, and from the Harvard Medical School in 1933. After serving twenty months as a House Officer at the Massachusetts General Hospital on the Medical Service, from July 1933 to February 1935, Mayo came to the University of California Medical School as a special graduate student in Medicine. For the next thirteen years, to July 1, 1948, Mayo progressed rapidly from positions as Research Assistant in Medicine, Instructor in Medicine and Physiology, Instructor in Medicine and Pharmacology, Assistant Professor of Medicine and Pharmacology, Associate Professor of Medicine and Pharmacology, and, on July 1, 1947, was promoted to a professorship in Medicine. For two years, 1942–44, Mayo served as Chairman of the Division of Pharmacology, succeeding Chauncey D. Leake and he lectured also in the College of Pharmacy. From 1944 to 1948, Mayo was Assistant Dean of the Medical School. In addition to a succession of appointments on the visiting staff of the University of California Hospital, Mayo served as Consulting Pharmacologist at the San Francisco Hospital, the Langley Porter Clinic and the Letterman General Hospital.

Dr. Soley became a Fellow of the American College of Physicians in 1948. He was a member of numerous and important medical societies, which are listed to show his wide range of interests and contributions: California Medical, American Medical, American Heart and California Heart Associations, Association for Study of Internal Secretions, American Society for Clinical Investigation, American Association for the Advancement of Science, American Physiological Society, Society for Experimental Biology and Medicine, Sigma Xi, California Academy of Medicine, American Federation for Clinical Research, Western Society for Clinical Research (Vice-President, 1946–47; President, 1947–48), and American Association for Study of Goiter.

It will be noted that Dr. Soley's rise in academic rank was spectacular. He brought to his work a scholarly and inquiring mind. His application to all problems in his wide field of interest was beyond the reach of most of us. He was a gifted teacher, a sound, careful research worker, who was at his best in collaboration with others. His interest in students was noteworthy. Many students came to him for help and guidance in professional and personal matters, and he inspired all of them to seek greater heights of accomplishment.

Dr. Soley's ability as an administrator and student advisor led to his selection as Assistant Dean. In this capacity he had an opportunity which prepared him for his last position, at The State University of Iowa College of Medicine.

Dr. Soley's scientific contributions were chiefly in the field of endocrinology. He became an expert in diseases of the thyroid. He made careful studies on exophthalmos in diffuse toxic goiter, initiated chemical studies on blood iodine in relation to functions of the thyroid and, with Joseph G. Hamilton, made the pioneer studies on radioactive iodine in thyroid disease. He made sound observations on the gas exchange in the hyperventilation syndrome. Among the fifty papers credited to him, there were very few which did not carry the names of others who collaborated with him. This gift of working with others to extract the facts and to present them in well documented form was a most inspiring example for all who had the good fortune to share in his work.

On July 1, 1948, Mayo resigned from the University of California Medical School to accept the position of Dean and Professor of Experimental Medicine at The State University of Iowa College of Medicine. William Bennett Bean, Professor of Medicine, has written an estimate of Dr. Soley's brief career at his new post, where death came tragically on June 21, 1949. This appeared as an editorial in *The Daily Iowan*, on June 25, 1949.

"'A VERY PARFIT GENTIL KNIGHT'

"Mayo Soley came to us with the fervor of high ideals and hopes that he might supply the college of medicine in Iowa with the leadership needed to attain excellence worthy of the people of the mid country of our land. Bringing with him the commingled pride and reserve of a New England heritage to which was added the enthusiasm of the West Coast, he epitomized the traits which have given greatness and luster to the nation.

"He had achieved distinction as a physician. He had done imaginative research of high originality as a student of the processes of disease. He had made his mark in the field of medical school administration.

"Motivated by a profound feeling for the patient and the student, the warmth of his presence made him a sympathetic teacher. Because he was always a student he was a superb clinician. His leadership was recognized by membership in the significant medical societies, and service on national committees and editorial boards.

"But this array of notable attainments is only the cold list of what a stranger might say in tribute. His warmth and color gave to them a meaning which kept him high in the affectionate regard of his fellows.

"He was the cherished center of a devoted family. He was a thoughtful and devoted friend. There was about him the style and elegance of the sunny side of the hill on a spring day. His energy and enterprise found outlets in varied sports in which he went beyond proficiency, for he was satisfied with nothing short of perfection.

"Into everything he put a prodigy of effort, carrying on his multitudinous tasks with verve and buoyancy. With high sense of duty, sound scholarship, keen intellect and ready wit he had at his command the mass of detail needed to direct a college of medicine. What he had achieved in the face of innumerable difficulties in one short year had won for him not only respect and admiration but the sympathetic support of his associates.

"With such qualities and character he brings to mind the grace and skill, elan and many-sidedness of the Elizabethan gentleman. Beyond anyone's thought he was impatient of delay and drove himself relentlessly but without bitterness to reach his goal. With so much of the path traversed he was suddenly overwhelmed, a martyr to his own idealism.

"'He was a very parfit gentil knight.'"

WILLIAM J. KERR, M.D., F.A.C.P.

DR. ALEXANDER L. LOURIA

Dr. Alexander Leon Louria, of Brooklyn, N. Y., died on May 22, 1949. He was born in Russia in 1890 and came to this country in 1896. He received his B.S. and his M.D. degrees from Columbia University, in 1910 and 1913. He served an internship in the Jewish Hospital, Brooklyn, from 1913 to 1915, and spent some time in 1920 and 1921 in postgraduate medical study in Germany. He became a member of the staff of Jewish Hospital, and at the time of his death was Clinical Professor of Medicine in the Long Island College of Medicine.

Dr. Louria was elected to Fellowship in the American College of Physicians in 1946. He was a former Trustee of the Medical Society of the County of Kings, and a past-President of the Williamsburg Medical Society.

Dr. Louria was one of the highly respected physicians in Brooklyn, and his untimely death is recorded with regret.

ASA L. LINCOLN, M.D., F.A.C.P.,
Governor for Eastern New York

DR. VICTOR FRANCIS CULLEN

Victor Francis Cullen, M.D., F.A.C.P., of Baltimore, Md., died on March 9, 1949. Born in Maryland on September 5, 1881, Dr. Cullen was a graduate of Rock-Hill College and the Johns Hopkins University School of Medicine. He later received the LL.D. degree from Mount St. Mary's College, Emmitsburg. Dr. Cullen served as interne and resident in St. Joseph's Hospital, Baltimore, became superintendent and medical director of the Maryland Tuberculosis Sanitorium in 1908 and served in this capacity and later as superintendent of the Tuberculosis Sanitaria of Maryland until 1946, when he retired.

Dr. Cullen was a Diplomate of the American Board of Internal Medicine. He became a Fellow of the American College of Physicians in 1930. He was a former president of the Medical and Chirurgical Faculty of Maryland and a former president and director of the National Tuberculosis Association.

Dr. Cullen was widely and affectionately known to the medical profession of Maryland. Though his administrative responsibilities were heavy, he made himself constantly available as a consultant in pulmonary disease to practitioners throughout the state. His interests in medicine extended beyond his special field. He gave unselfishly of his time as a prominent member of the Committee on Medical Care to the development of the state supported program of medical care for the indigent and medically indigent in the rural counties of Maryland. A man of high ideals, great generosity and untiring energy, he spent his strength for others and in return was much beloved.

DR. RALPH PEMBERTON

With the death of Dr. Ralph Pemberton on June 16, 1949, the College has lost one of its old and distinguished Fellows.

Dr. Pemberton's medical interests were varied. Internal medicine, neurology and chemistry claimed his interest at various periods of his medical life. It was really his interest in chemistry which led him into the study of arthritis, the subject with which his name will always be associated. It is altogether proper to say that he played an important role in introducing into the study of this subject the orderly, integrated, and intensive investigation which it is now receiving.

Dr. Pemberton was born in Philadelphia on September 14, 1877. He graduated in medicine from the University of Pennsylvania in 1903. In 1911 and 1912 he did postgraduate work in Germany. Incidentally, almost the last thing that he wrote was

a quite charming account of his student days in Germany as he recalled them in his later years. Some of the academic positions which he held were Assistant Visiting Neurologist, Philadelphia General Hospital, 1905–1908; Woodward Fellow in Physiological Chemistry, William Pepper Laboratory, Hospital of the University of Pennsylvania, 1908–1910; Instructor in Medicine, University of Pennsylvania School of Medicine, 1909–1910; Visiting Physician and Director of Department of Clinical Chemistry, Presbyterian Hospital, 1913–1933; Assistant Professor of Medicine, University of Pennsylvania Graduate School of Medicine, 1928–1931, and Professor of Medicine, 1931–1949.

The many active and honorary positions and offices which he held testify to the importance in which his contributions to the study of arthritis were held. He was a member of the Council on Physical Therapy, American Medical Association; President, Ligue Internationale Contra le Rheumatisme; President, Pan American League for the Study and Control of Rheumatic Diseases; recipient of the Distinguished Service Gold Key of the American Congress of Physical Medicine; Honorary Fellow of the Royal Society of Medicine, London; and Honorary Member of the Societatea Anatomo-Clinica, Bucharest.

Dr. Pemberton served as Major in the U. S. Army Medical Reserve Corps in World War I. He became a Fellow of the American College of Physicians in 1923.

THOMAS M. MCMILLAN, M.D., F.A.C.P.
Governor for Eastern Pennsylvania

COLONEL JOHN WILLIAM MEEHAN

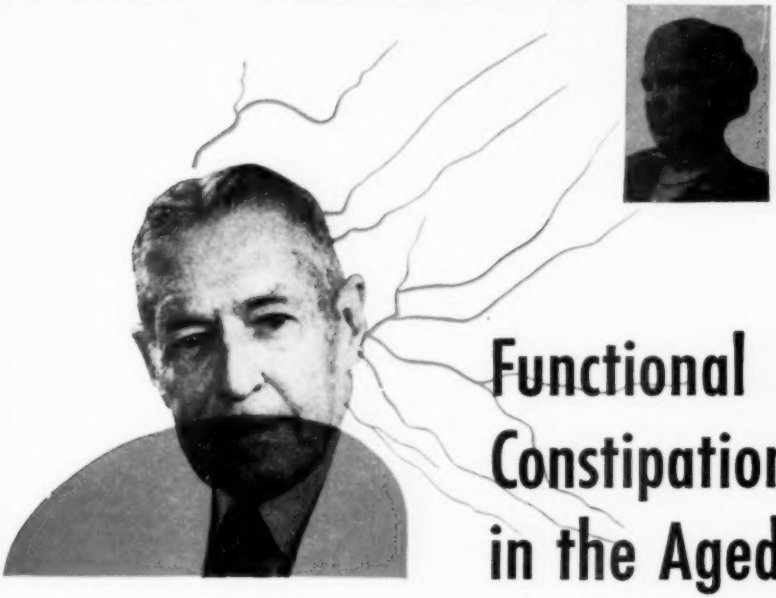
Col. John William Meehan, F.A.C.P., (MC), U. S. Army, Retired, Washington, D. C., died May 28, 1949. Col. Meehan was born in Nebraska on May 1, 1884, attended St. Mary's College and received therefrom his A.B. and A.M. degrees. He graduated from Creighton University School of Medicine, Omaha, in 1908. He pursued postgraduate work in Public Health at Johns Hopkins University School of Hygiene and Public Health. In 1926, he entered the Medical Corps of the U. S. Army and served in many parts of the world during his extended tour of duty. His primary interest was in the field of Public Health and Vital Statistics. He served with distinction and had been an honored Fellow of the American College of Physicians since 1930.

COLONEL GEORGE ALFRED SKINNER

Colonel George Alfred Skinner, (MC), USA, Retired, Berkeley, Calif., died May 15, 1949, being accorded a military funeral at the Presidio of San Francisco. Colonel Skinner had been a patient at the Letterman General Hospital for several months.

He was born at Osage, Iowa, June 11, 1870; graduated from the Rush Medical College in 1892, and interned at Cook County and St. Luke's Hospitals in Chicago. He entered the Medical Corps of the U. S. Army in 1896, and served on many important assignments at home and abroad. He was in the Philippines during the Spanish-American War; during World War I he commanded a thirty-thousand bed hospital in France, and received decorations of the United States and of France. Thereafter he served as Surgeon at Camp Lewis, Wash., for seven years, and was Chief Medical Officer in the Seventh Corps Area, Omaha, when he retired. Subsequently, he served as Professor of Public Health at the University of Nebraska. He had been a prolific writer, and won the Welcome Prize of $500.00 and a gold medal for an essay on sanitation. He lived at Berkeley, Calif., from 1938 forward.

Colonel Skinner was a pianist and organist, composed music and wrote for music publications. He was a Mason, a member of the California Writers' Club, Association of Military Surgeons of the United States, American Heart Association, a Fellow of the American Medical Association, and had been a Fellow of the American College of Physicians since 1933.



Functional Constipation in the Aged

"Constipation is very frequently found in people of climacteric age,.... In the vast majority of patients, constipation is probably due to improper habits, diet, or gastrointestinal disorders."*

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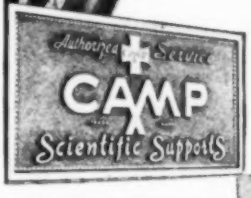

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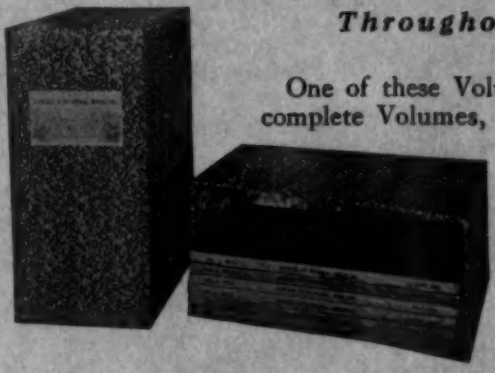

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